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STUDIES

FROM THE

PHYSIOLOGICAL LABORATORY

OF

OWENS COLLEGE.

EDITED BY

ARTHUR GAMGEE, M.D., F.R.S.,

BRACKENBURY PROFESSOR OF PHYSIOLOGY.

Cambridge:

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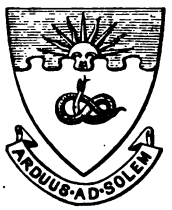

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1877

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TO

ROBERT PLATT, Esq.,

OF

DUNHAM HALL,

WHO BY THE FOUNDATION OF THE SCHOLARSHIPS

WHICH BEAR HIS NAME TESTIFIED HIS INTEREST IN THE

ADVANCEMENT OF PHYSIOLOGICAL SCIENCE,

THIS FIRST COLLECTION OF

STUDIES FROM THE PHYSIOLOGICAL LABORATORY

OF OWENS COLLEGE IS DEDICATED BY

THE EDITOR.

CONTENTS.

PAGE

Prof. GAMGEE and Mr LARMUTH, On the Action of Vanadium upon the Intrinsic Nervous Mechanism of the Frog's Heart . . 1

Mr LARMUTH, On the Poisonous Activity of Vanadium in Ortho-, Meta-, and Pyro-Vanadic Acids 17

Prof. GAMGEE, Mr PRIESTLEY and Mr LARMUTH, On the Difference in the Poisonous Activity of Phosphorus in Ortho-, Meta-, and Pyro-Phosphoric Acids 21

Prof. GAMGEE, Mr PRIESTLEY and Mr LARMUTH, On the Action of Pyro-Phosphoric Acid on the Circulation 39

Mr PRIESTLEY, Observations on the Physiological Action of Chromium 51

Mr BROOKE and Mr HOPWOOD, On the Changes in the Circulation which are induced when the Blood is expelled from the Limbs by Esmarch's Method 68

PREFACE.

It is my intention henceforward to issue from time to time in a collected form the results of the work done in our Physiological Laboratory, thus emulating the example which has long been set by many of the laboratories of continental Europe, and especially by that of Leipzig, and which has recently been followed in England by the laboratories of University College and of the University of Cambridge.

Had not economical reasons prevented us, this first number would include a reprint from the *Philosophical Transactions* of Mr Priestley's memoir 'On the physiological action of Vanadium;' as it is, a copy of that paper accompanies these studies, and is to be looked upon as forming an integral part of them.

Amongst the work done in our laboratory during the last year was a research undertaken by Mr Priestley on the innervation of the batrachian lymph-hearts, at a time when, unfortunately, we were in ignorance of the researches conducted on this subject by the more recent investigators, and especially by Goltz and Suslowa. The agreement between their results and Priestley's was so great as to render a full publication of his results unnecessary; the following remarks upon them may however be made.

There is no doubt that the ordinary rhythmical motions of the lymphatic hearts of frogs depend upon the integrity of certain spinal centres. Of these the anterior is situated, according to all observers, about the level of the third vertebra. The posterior in Rana temporaria is, according to Mr Priestley, opposite the sixth vertebra, and not opposite the eighth, as the majority of writers following Volkmann have asserted. These motor centres are controlled by an inhibitory centre situated not in the medulla oblongata, the place assigned to it on somewhat insufficient evidence by Goltz,

but in the optic lobes, as was beautifully demonstrated by Suslowa and quite independently ascertained by Priestley; this inhibitory centre is in continual slight action, since its separation from the motor centres is followed by sustained acceleration of the lymph-hearts. Mr Priestley is not in a position to criticize Suslowa's statements as to the reflex relations of the higher centre through the sympathetic system with peripheral nerve terminations, nor is he prepared to endorse Suslowa's assertion that entire separation from the nervous centres is invariably followed by stoppage of the lymphatic hearts.

Two facts which were noticed in Mr Priestley's experiments, and which had altogether escaped the observations of previous workers, may be specially mentioned. 1. Anœsthetics, as chloroform and ether, abolish the activity first of the higher (inhibitory) centre, and afterwards of the lower, bringing the lymph-hearts to rest. In the first stage of their action these anœsthetics produce, therefore, the same result as follows division of the cord high in the cervical region. 2. Curare injected in small quantities into the dorsal lymph-sac swiftly causes stoppage of the posterior lymph-hearts, sometimes even before the power of voluntary motion has ceased; hence it would appear that the motor end-organs in the muscular walls of the lymph-sacs resemble those of voluntary muscle rather than those of the blood-heart. Curare dropped upon lymph-hearts beating after *complete* separation from the nerve-centres causes their almost instant stoppage.

ARTHUR GAMGEE.

JAN. 5TH, 1877.

From the *Journ. of Anat. and Phys.*, Vol. XI.]

ON THE ACTION OF VANADIUM UPON THE INTRINSIC NERVOUS MECHANISM OF THE FROG'S HEART.

By PROFESSOR ARTHUR GAMGEE, M.D., F.R.S., AND LEOPOLD LARMUTH, *Platt Physiological Scholar in Owens College.*

IN his memoir "On the Physiological Action of Vanadium," (*Philosophical Transactions*, 1875) J. Priestley recapitulates the facts which he has ascertained with reference to the action of this poisonous metal on the circulation in the following manner.

"A consideration of the experiments shews that the influence of vanadium upon the circulation is three-fold. In the first place, there is a diminution of blood-pressure, which, however, is not quite continuous, but is marked by intervals in which there is a tendency to regain the former height. Then alternate rises and falls take place with considerable regularity. In the second place, there is a disappearance of the respiration curves. And in the third place, there is irregularity and diminution of rapidity of the pulse, which, like the fall of the blood-pressure, is not quite regular. In the case of injection into veins there was scarcely time, owing to the rapidity of death, for the development of the marked fluctuations noticed when injection was hypodermic.

"The disappearance of respiration curves can only be due to some alteration of the vaso-motor centre, whose oscillations of activity are the cause of them. The marked fall of blood-pressure might be due to one, or more, of the following circumstances: 1, Paralysis of the vaso-motor centre; 2, peripheral irritation of depressor nerves; 3, relaxation of arterial tonus due to other causes than vaso-motor paralysis; 4, weakening of the heart's action. The alteration of the pulse may be

caused by 1, some action upon the vagi; 2, poisoning of intra-cardiac centres; 3, poisoning of muscular substance of heart; 4, diminution of blood-pressure. As previous division of the vagi does not seem in the least to alter the circulatory effects of poisoning by vanadium, it is clear that none of these effects can be attributed to the action on the vagi. It is, moreover, evident from experiments detailed elsewhere in this paper, that there is no poisoning of the muscular substance of the heart itself.

"Further, the fact that vanadium does not paralyse unstriped muscles in other regions of the body (as in the intestines) renders it probable that there is no direct action upon the muscular walls of the arteries. We may therefore at once eliminate both these possibilities from the question. It will be seen on comparison that the fluctuations in blood-pressure and in pulse are only sometimes coincident; neither will, therefore, serve as sufficient explanation of the other, although the effects may be partially due to their inter-action. There remains, therefore, the vaso-motor system of nerves, with the depressors, and the intra-cardiac nervous mechanism, to which we must look for the chief explanation of the phenomena under consideration.

"From the experiments in which the cord was divided in the neck, we gather that the effects of vanadium-poisoning upon the pulse occurred as usual, while the diminutions and fluctuations in blood-pressure were no longer visible, being indeed replaced by a rise. As in those experiments the vaso-motor centre, the accelerators and the vagus-centre terminations were eliminated (the vagus-terminations by means of the curari which was injected), we are driven to the conclusion that the depression and fluctuations of blood-pressure are for the most part due to some action of the poison on the vaso-motor centre; and that the irregularities of heart-beats are caused by an affection of intra-cardiac ganglia. The former conclusion is strongly confirmed by the disappearance of respiration-curves, which must be due to vaso-motor mischief, and by the fact that other centres in the cord are acted on by vanadium: hence it seemed hardly necessary to perform any special experiments after elimination of the depressors. The latter

conclusion is fully borne out by Experiment LIII., on a frog, where the usual diminution followed in a heart which was directly observed after the removal of all extra-cardiac nervous influences. The rise of blood-pressure which follows injection into the veins of rabbits, whose spinal cord has been cut, is considered to be due to the greater vigour of the heart, which was noticed."

Thoroughly satisfactory as were the investigations on the effects of vanadium in the circulatory system of warm-blooded animals, it appeared that additional experiments were desirable in order to investigate more closely the precise mode in which vanadium affects the intra-cardiac nerve-centres, and we therefore undertook an examination of the action of vanadium upon the frog's heart.

In Priestley's researches the compound of vanadium employed was invariably the sodium ortho-vanadate, Na_3VO_4, of which standard solutions containing exactly 5 per cent. of V_2O_5 were used. In the present research, for reasons which will appear in the sequel, the sodium salts of the ortho-, meta-, and pyro-vanadic acids were employed at various times, the solutions always being neutral, and containing a quantity of vanadium corresponding to 5 per cent. of V_2O_5.

The three compounds employed have the following formulæ:

1. Meta-vanadate of Sodium, $NaVO_3$.
2. Pyro-vanadate of Sodium, $Na_4V_2O_7$.
3. Ortho-vanadate of Sodium, Na_3VO_4.

The compounds of vanadium, and the standard solutions used throughout were prepared under the direction of Professor Roscoe, F.R.S., by Mr Taylor, Demonstrator of Metallurgy in Owens College.

In some of our experiments Rana esculenta was employed, but in the greater numbers Rana temporaria, in a few the large American Bull-frog.

Methods of investigation.

In some of our experiments the movements of the hearts of pithed frogs were observed, *in situ*, with the eye, and the

solution of which the poisonous action was being investigated was injected through the abdominal vein. In some few experiments the poisonous solution was applied to the external surface of the heart. In some cases, as in the experiments undertaken to ascertain the comparative poisonous activity of the three vanadic acids, the poison was introduced into the lymph-sacs of frogs, the heart being exposed and watched after the general paralytic phenomena which are induced by the compounds of vanadium had become developed. In the greater number of experiments a modification of the method used by Ludwig and Coates was employed, of which the essential feature consisted in the serum being kept in a state of circulation by means of the frog's heart, except during the time when tracings were being taken. The frog was supported on a horizontal plate, and its vena cava connected with a flexible tube leading to a reservoir of serum, the height of which could be accurately regulated. This reservoir consisted of a short test-tube, into the bottom of which a finer tube (for connection with the above-mentioned flexible tube) had been fused. Supported directly over the mouth of this test-tube was a thermometer, the bulb of which was immersed in the serum in the reservoir. The aorta was connected with a long glass tube attached to a gauge precisely similar to that used by Coates. The same limb of the gauge was connected with a long flexible tube terminating in a fine glass nozzle, which was carried round and fixed against the thermometer at a height of about 2 inches, or rather more, above the surface of the serum in such a manner that, as the serum was driven through the nozzle, it spread over the thermometer-stem in a thin film which flowed down to the reservoir, thus presenting a very large surface for aëration. When tracings were about to be taken, the tube from the proximal limb leading to the aërating nozzle was guarded by a clip, whereupon the blood-pressure raised the mercury in the distal limb, and movements were recorded.

The serum employed in the majority of the experiments was that of the rabbit. The capacity of the serum reservoir was 5 cub. cents.

Exp. I. (3 | 2 | 76.) A frog (R. esculenta) was pithed and the heart prepared for Coates's experiment. Reddish sheep's serum employed.

H. M.

2 . 20. Heart connected with serum-reservoir and gauge.

3 . 20. Normal tracing taken. Heart beats vigorously, between 5 and 6 times per 10 seconds.

3 . 21. Circulation of poisoned serum commenced. The serum was prepared by mixing 1 volume of standard solution of sodium ortho-vanadate (containing 5 per cent. of V_2O_5), with 50 volumes of sheep's serum.

3 . 24. A tracing taken. Contractions of the heart are much slower, 1 in 3 seconds. The contractions are, however, perfect and regular.

3 . 30. Another tracing taken. Contractions not as vigorous as before, but occur with the same frequency. The ventricle appears to be abnormally contracted at apex. A vermicular contraction of the ventricle occurs at intervals; this runs from base to apex, and pinches off, as it were, the ventricular apex. The auricles are contracting normally.

3 . 38. Another tracing taken. No marked change.

3 . 55. Vermicular contractions of ventricle very marked; the ventricle contracts sluggishly.

4 . 25. Ventricles still contracting, though very inefficiently.

4 . 40. Tracing taken; the rise of the mercury in the manometer at each systole is indicated in the tracing by slight waves in the line traced by the pen.

Exp. II. (4 | 2 | 76.)

12 . 15. Rana esculenta decapitated, pithed, and heart prepared.

12 . 30. Pure serum allowed to flow through the heart.

12 . 53. Heart contracting vigorously, once in 2·75 seconds.

1 . 48. Normal tracing taken. Contractions slower, but vigorous, 1 in 5 seconds.

2 . 5. Another tracing taken. Agrees with the preceding. Serum poisoned with solution of Na_3VO_4 (1 volume of standard solution of the poison to 50 of sheep's serum) allowed to circulate through the heart.

2 . 10. Contraction of heart slower, though more vigorous than before.

2 . 15. Peristaltic contraction of ventricle, the systole of which is becoming more sluggish.

2 . 30. Contraction of ventricle very slow and imperfect, so that a satisfactory tracing cannot be obtained.

2 . 45. Auricles are contracting slowly, ventricle is in a state of permanent contraction; occasional vermicular contractions of ventricle.

3 . 0. Ventricle is contracting peristaltically, once in 30 seconds; auricle contracting once in 10 seconds.
3 . 15. Occasional slight vermicular contractions of ventricle, about once in 45 seconds; auricle contracts once in 15 seconds.
4 . 0. Auricles still contracting feebly; only very occasional slight vermicular contractions of ventricle.

Exp. III. Rana temporaria. Circulation of rabbit's serum, at T. 14° C, through heart.

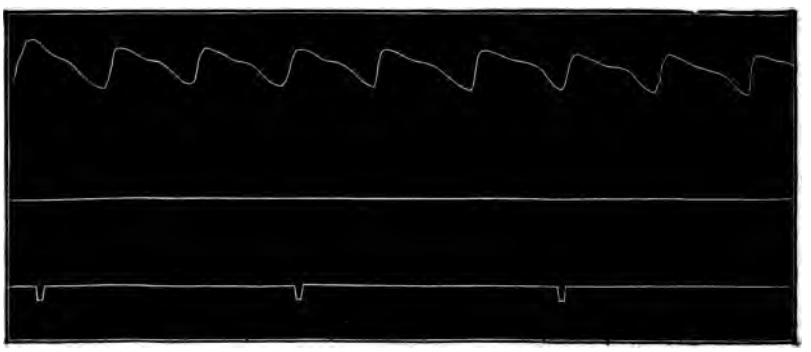
H. M.
2 . 40. Frog prepared.
3 . 0. Aorta has been connected with the manometer, heart has been washed out with reddish rabbit serum, and is contracting fully and vigorously.
4 . 0. Poisoned serum allowed to circulate. As it reached the heart the organ commenced to beat a little more rapidly.
4 . 5. Heart contracting once in 2 seconds.
4 . 10. Vermicular contractions of ventricle. One contraction of ventricle to 3 of auricles.
4 . 15. Tracing indicates that the heart is contracting 1 in 2·2 seconds, much less vigorously than before.
4 . . 30. Contractions more prolonged and feeble.
4 . 40. Auricles contracting once in 7 seconds; ventricle feebly, once in 20 seconds.

(Experiment not continued).

Exp. IV. (8 | 2 | 76.) Rana temporaria. Rabbit's serum at T. 16° allowed to circulate.

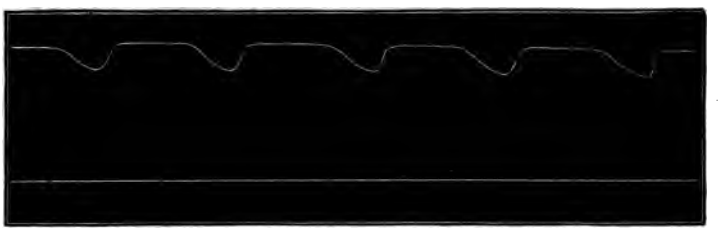
1 . 0. Frog prepared.
1 . 20. All connections have been made. Heart has been washed out with rabbit's serum; is beating vigorously.
1 . 45. Normal tracing taken. Heart beats fully 6 times in 10 seconds.

Fig. 1.



2 . 0. Another tracing, exactly similar to the preceding, taken.
2 . 15. Circulation of poisoned serum commenced (1 volume of standard solution of Na_3VO_4 to 50 of serum).
2 . 20. The characters of the contractions, and therefore of the tracings, have altered considerably; they have become much less frequent, the force of the contraction has diminished, whilst the length of the systole has increased in a marked manner (Fig. 2).

Fig. 2.

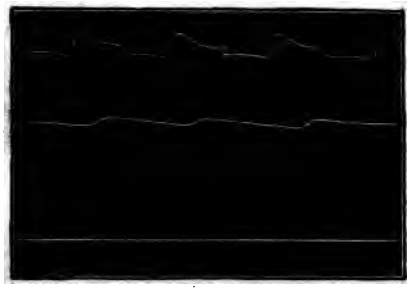


2 . 40. Tracings taken since the last shew exactly the same characters; the ventricle is nearly always in a state of systole, the diastolic intervals being very short.
3 . 0. Since the last note the heart appears to have commenced to recover from the effects of the poison, the contractions of the ventricle becoming more complete and more rapid.
3 . 40. Heart appears to have recovered completely, contracting four times in 10 seconds.
3 . 45. A fresh quantity of the standard solution of Na_3VO_4 added to the serum in the reservoir. The mixture then consisted of 2 volumes of solution of the poison to 50 volumes of serum.
3 . 47. The ventricle is in a state of strong and persistent contraction. The auricles contract slowly.
3 . 50. It has been impossible to obtain any tracing since the poisoning. Auricles slowly pulsating.
4 . 0. Ventricle now at rest in diastole; some portions of the ventricles are, as it were, pinched off by local contractions. Auricle and sinus venosus contracting sluggishly.

Exp. V. (11 | 2 | 76.) Rana temporaria. Rabbit's serum at a temperature of 15° C allowed to circulate through heart.

2 . 45. Frog decapitated and prepared for experiment.
3 . 0. Connections have been made, and heart washed out with serum.
3 . 15. Normal tracing taken (Fig. 3).
3 . 42. Heart has been beating with perfect regularity, and a tracing taken now is exactly similar to that taken at 3.15. Poisoned serum (1 volume of Na_3VO_4 solution to 50 of rabbits' serum) allowed to circulate.

Fig. 3.



3 . 44. Ventricle is in a state of strong and persistent contraction; auricles contracting rhythmically.

3 . 47. A tracing taken; the elevations are due to the auricular contractions, as the ventricle is not beating (Fig. 4).

Fig. 4.

3 . 49. After a short time the ventricle has commenced to contract again vigorously; contractions recur rhythmically for 5 minutes, then cease, the ventricle remaining in a state of systole.

4 . 0. Ventricle at rest in a state of contraction. Auricles contracting normally.

4 . 5. By raising the pressure of serum in the heart, the ventricle commences to contract. The contraction runs from base to near apex, but stops short so as to pinch off, as it were, a portion of the apex. Upon diminishing the pressure the ventricle ceases to contract in systole.

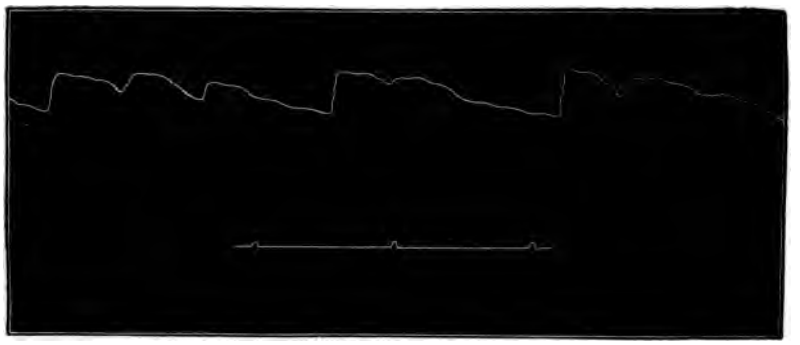
4 . 15. The ventricle contracts only occasionally, whilst the auricles contract with regularity.

4 . 17. The condition of the heart is well shewn by the annexed tracing (Fig. 5). Contractions of the ventricle succeed each other slowly, in groups of two or three, and then a prolonged diastole follows.

4 . 55. The heart is recovering somewhat from the effects of its first poisonous dose.

5 . 10. Although there are still evidences of the action of vanadium upon the heart, it is determined to increase the strength of the poison.

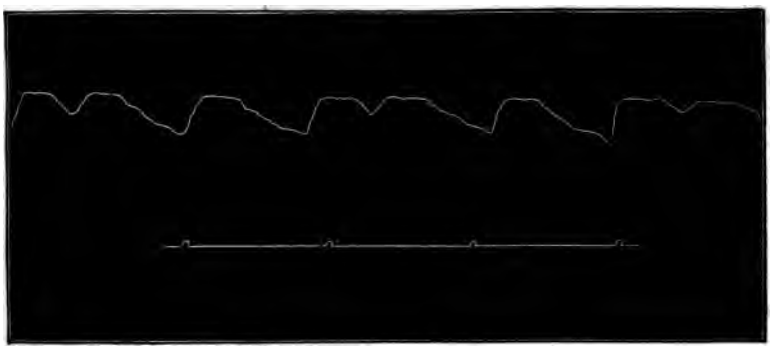
Fig. 5.



5 . 15. One more volume of the solution of $Na_3 VO_4$ added to the serum.

5 . 16. After two contractions of the ventricle a pretty long pause occurs; then generally a single slow contraction; followed again by two contractions, thus:

Fig. 6.



5 . 20. Ventricle in a persistent semi-contracted state; *i. e.* diastole never complete.

Observations discontinued.

Remarks.—The five experiments which have preceded illustrate the influence exerted by a *small* dose of vanadium when mixed with serum, and allowed to circulate through the separate frog's heart. In them, as has been mentioned in the notes of the individual experiments, one volume of a weak solution of sodium ortho-vanadate was mixed with 50 volumes of reddish rabbit's serum; as the solution of vanadate contained a quantity of vanadium corresponding to 5 per cent. of $V_2 O_5$, the percentage of the poisonous metal contained in the poisoned serum was ·098. In the experiments which follow the effect of a dose twice as large are shewn.

Exp. VI. (15 | 2 | 76.) Rana temporaria.

H. M. Rabbit's serum at T. 18° C. employed.

2 . 0. Frog decapitated and heart prepared for the experiment.
2 . 45. Normal tracing taken; heart is beating vigorously.
3 . 0. Circulation of poisoned serum commenced. (1 volume of standard solution of $Na_3 VO_4$ mixed with 25 volumes of serum.)
3 . 3. Ventricle contracting very slightly at long intervals.
3 . 5. Apex of ventricle firmly pinched off; the rest of the ventricle in a state of distension; auricles contracting slowly.
3 . 25. Ventricle is firmly contracted; auricles are contracting slightly and sluggishly.
4 . 20. Ventricle as before. Auricles are contracting about once every 20 seconds.

No tracings could be obtained after the poisoning; the normals have therefore not been copied.

Exp. VII. (15 | 2 | 76.) Rana temporaria.

Rabbit's serum at T. 18° employed.

4 . 20. Frog's heart prepared; pure serum allowed to circulate.
4 . 30. Normal tracing taken. Heart is beating vigorously and regularly.
4 . 45. Another tracing taken; allowed poisoned serum (1 : 25) to flow through.
4 . 47. Ventricle beating feebly; does not relax completely during diastole; auricles are contracting quite normally.
4 . 50. Ventricle strongly contracted; auricles beating feebly.
5 . 5. Auricular contractions continue, though feeble.
5 . 30. Ventricle still contracted; auricles still beating.

In this experiment it was again impossible to obtain any tracings after the poisoning.

Exp. VIII. (21 | 2 | 76.) Rana temporaria.

H. M. Rabbit's serum used. Temperature not known.

3 . 20. Frog's heart has been prepared and washed out with rabbit's serum.
3 . 30. Normal tracing taken.
3 . 45. Poisoned serum allowed to circulate (1 of standard solution of $Na_3 VO_4$ to 25 of serum).
3 . 46. Ventricle contracting vigorously.
3 . 46.5. Ventricle in a state of complete and continuous contraction; auricles beating slowly.
3 . 50. Heart in same state as before, auricles beating slowly.
4 . 30. Heart in a state of distension; neither auricles nor ventricles beating; upon pinching, slight contraction of the ventricle is produced.

Exp. IX. (18 | 2 | 76.) Rabbit's serum. T. 19°.

3 . 35. Heart of rana temporaria has been prepared and rabbit's serum allowed to circulate. Heart beats normally.
3 . 45. Normal tracing taken.
3 . 50. Poisoned serum allowed to flow through heart (1 of standard solution of Na_3VO_4 to 24 of serum).
3 . 52. Ventricle firmly contracted. Auricles beating normally.
4 . 30. Condition of heart exactly the same as before.
4 . 50. Ventricle less relaxed than before; auricles beating as at first.
5 . 0. Ventricle fully distended and at rest. When pinched it makes a single sluggish contraction; auricles contract normally.
6 . 0. Ventricle distended; a local contraction of ventricle follows pinching: auricles contracting normally.

Exp. X. (21 | 2 | 76.) Rana temporaria.

3 . 20. The frog having been decapitated and pithed, heart prepared and connected with Coates' apparatus. Pure rabbit's serum allowed to circulate at first.
3 . 30 and 3 . 40. Perfectly normal tracings taken. Heart beating regularly and vigorously.
3 . 45. One volume of standard solution of Na_3VO_4 mixed with 25 volumes of the serum.
3 . 46. Very vigorous contraction of ventricle.
3 . 46.5. Ventricle in a state of complete and persistent systole.
3 . 50. Heart in same state as before; auricles beating slowly.
4 . 50. Heart in a state of distension; neither auricles nor ventricles are beating. Upon pinching the ventricle slight contractions follow.

The ten experiments which have preceded illustrate in a very satisfactory manner the phenomena which are observed when serum poisoned with a soluble vanadate circulates through the excised heart of the frog.

When the serum contained the poison in the proportion of 0·098 per cent. of V_2O_5 it was observed that the force of the ventricular systole was very much diminished, that the ventricle passed into a state of persistent contraction for a time, or, in many cases, that whilst portions of the ventricle were in a state of diastole others were firmly contracted. Generally, however, such a proportion of the poison did not kill the heart, and the effects which were at first produced appeared gradually to be recovered from. On then increasing the quantity of poison in

the circulating serum the ventricle was usually, but not always, brought to a complete standstill in a state of firm contraction.

When the amount of the poison contained in the serum is about twice as large, viz. amounts to 0·192 per cent., the effects produced follow much more rapidly. Usually within one or two minutes the ventricle stops in a state of rigid contraction, whilst the auricles continue their rhythmical movements, enfeebled however, for a considerable length of time.

The reader will not fail to perceive that the phenomena which have yet been described are in essential particulars the same as occur in poisoning by digitalis. Like digitalis, vanadium seems to cause a slowing of the heart by abridging the diastolic period, *i.e.* by lengthening the systole, and to bring the ventricle to a standstill in systole. It is to be observed that not unfrequently the heart which has been poisoned by vanadium and the ventricle of which has been for a considerable time in a state of rigid contraction, becomes completely relaxed.

In the closer study of the action of vanadium on the frog's heart there were two sets of experiments which appeared likely to prove of special interest: the first consisting in observing the effects of excitation of the vagi on the poisoned heart; the second in ascertaining whether atropia modified in a special manner the action of the drug.

Exp. XI.

H. M.

12 . 20. Large Canadian bull-frog pithed and prepared for Coates's method. Vagus exposed and ligature passed beneath it. Reddish rabbit serum used in the experiment. After the left aorta had been connected with the gauge, platinum electrodes connected with the secondary coil of Du Bois Reymond's apparatus were placed under the right vagus. With the secondary coil at 40 Cm there was slight slowing; at 30 Cm the effect was greater, but the heart did not stop; at 20 Cm the heart stopped at once.

12 . 45. A normal tracing taken. The temperature of the serum circulating is 20·5° C.

12 . 54. The pure serum replaced by serum mixed with $\frac{1}{25}$th of its volume of standard solution of $Na_4V_2O_7$.

12 . 55. Ventricle observed to be abnormally contracted; auricles beating normally.

12 . 56. Ventricle completely and firmly contracted; at intervals

complete dilatation of circumscribed portions, the apex, for instance, being at times completely dilated and pinched off.

12 . 57. Ventricle still strongly contracted. Vagus excited; secondary coil at 20 Cm. Auricles cease pulsating but ventricle remains *firmly* contracted.

1 . 0. Right vagus again excited; complete stoppage of auricle, but no relaxation of ventricle.

1 . 1. Auricles alone pulsating; at intervals complete local dilatations of ventricle take place.

1 . 5. Heart still in same condition as before.

1 . 10. Ventricle completely and persistently contracted; auricles pulsating slowly but otherwise normally. Vagus irritated; auricles stop but ventricle is not affected.

1 . 13. Auricles are beating 9 times in 30 sec.; ventricle still contracted.

1 . 20. Auricles contracting 6 times in 30 sec.; ventricle contracted as before.

1 . 25. Ventricle firmly and completely contracted; small portions still dilated as before; auricles beating slowly but regularly. On exciting the vagus auricles stop but ventricle does not relax. During excitation the local dilatations of ventricle do not occur at all, the whole ventricle being firmly contracted.

1 . 31. To the poisoned circulating serum one drop of a ·5 p.c. solution of atropin sulphate was added.

1 . 35. On exciting the vagus no stoppage of the auricles takes place; ventricle still contracted though the local dilatations are somewhat larger.

1 . 40. Vagus excited; secondary coil full up to primary. No stoppage of the auricles. Ventricle firmly contracted.

1 . 45. Auricles beating 8 times in 30 seconds. No stoppage on exciting vagus; secondary coil at 0 Cm.

1 . 50. Ventricle becoming partially distended and not pulsating. Auricles contracting 5 times in 30 seconds. No stoppage on exciting the vagus.

2 . 0. Ventricle further dilated; not pulsating; mechanical and electrical stimulation produce no contractions; auricles still pulsate feebly and not arrested by powerful excitation of the vagus.

This was the only experiment in which excitation of the vagus was practised after poisoning by vanadium; the results which it yielded were, however, so positive that it appeared useless to repeat it.

This experiment proves, most conclusively, that after contraction of the ventricle of the frog's heart has been induced by vanadium, relaxation of the heart cannot be induced by exciting the vagus. It however teaches us that this is not due to any paralysis of the trunk of the vagus nor of its terminations, for

when excited it was able efficiently to inhibit the auricular movements, until atropia acted upon the heart, when the inhibitory mechanism was readily paralyzed, without any modification in the effects of vanadium upon the heart being induced.

In two sets of experiments, which for the sake of brevity are not quoted, the influence of atropia in modifying the action of vanadium was examined. The same quantity of a standard solution of sodium pyro-vanadate was injected into the abdominal vein of two frogs, one of which had been atropized. In both sets of experiments the result was exactly the same.

In another experiment the heart was prepared for Coates' method, and rabbit's serum poisoned with atropia was allowed to circulate through it. After obtaining a normal tracing the serum was poisoned with solution of sodium pyro-vanadate (1 volume of standard solution to 26 of serum), when the normal effect of vanadium was induced, viz. stoppage of the ventricular movement in systole.

In commencing the discussion of the mode in which the changes which have been described are brought about, it appears natural to enquire whether they are due to an action of vanadium upon the muscular substance of the heart or upon its intrinsic nervous mechanism, or upon both.

In the case of digitalin, veratria, and even antiar, it has been advanced that the state of rigid contraction of the ventricle which is induced by these drugs and which usually passes directly into rigor, is due to an action which they exert upon the protoplasmic substance of the heart, for these poisons are known to affect voluntary muscle, and therefore an action upon the muscular tissue of the heart is intelligible. Even these drugs cannot be considered to exert their action upon the heart merely by affecting its muscular structure, for whilst their ultimate effect on the ventricle is nearly the same, there appear to be in each case distinctive phenomena which can only be explained by supposing that they affect in different manners or more or less profoundly the nervous structures which are associated with the contractile elements. That their action is one which at first affects nervous rather than contractile elements, appears indeed obvious from the fact that all these poisons bring the ventricle to a standstill long before they affect the

auricle; in the case of antiar the auricle actually beats more powerfully after the action of the poison than before[1]. Now a poison which acted primarily upon the muscular structure of the heart would presumedly exert its action more readily upon the thin-walled auricles than upon the more fleshy ventricle. It is, however, without doubt a most difficult task, in these cases, to unravel the muscular and nervous effects so as to be able with anything like precision to discover how great a share is to be attributed to an impairment of the properties of the muscular tissue, and how much is due to an alteration in the action of the nervous mechanism proper.

In the case of vanadium the researches of Priestley prove very conclusively that whilst acting injuriously upon and ultimately killing voluntary or involuntary muscles immersed in solutions of its compounds, vanadium is not properly a muscular poison, *i.e.* after death has been induced by a compound of vanadium the contractility of muscle is found to be unaffected, and the amount of work done by such muscles does not differ from that done by the same muscles of other frogs not killed by vanadium[2]. Upon which of these two sets of facts shall we rely in interpreting the phenomena induced in the heart when it is fed with serum poisoned by vanadium? The majority of persons will probably say that the first referred to, which prove that a solution of vanadium when acting directly upon a muscular structure affects its irritability, are most conclusive, and that we should, *à priori*, expect that when investigated by the method of Ludwig and Coates an action of vanadium upon the heart would be discovered, and that a great part of that action would be referable to a poisoning of the contractile element.

Such indeed is our own opinion—vanadium, at any rate when present in quantity in the blood or serum circulating through the heart, doubtless acts as a poison of the contractile tissue of the organ; though this cannot, however, be considered to be its only action, for if it were, how could we explain the

[1] Some effects of Upas Antiar on the Frog's Heart, by M. Foster, M.D., F.R.S., *Journal of Anatomy and Physiology*, Vol. x.

[2] A muscular poison may be defined as one which, in exerting its toxic action, *necessarily* impairs muscular contractility; this impairment is best measured by ascertaining, first, the duration and character of contraction, and secondly, the power of doing work. A. G.

continued action of the auricles long after the ventricle has been arrested?

It has been shewn that vanadium induces a permanently contracted condition of the ventricle, which ceases to beat, whilst the auricles pulsate more slowly than normally, but yet with regularity. This contracted condition of the ventricle differs from that induced by digitalis in two important particulars: firstly, it does not usually pass into rigor mortis, the heart becoming frequently dilated when it dies; secondly, the contracted condition of the ventricle is not affected by irritation of the vagus, though this nerve retains its power of inhibiting the auricles.

In poisoning by vanadium it is obvious that there is no affection of the terminations of inhibitory nerves in the heart, and no affection of the inhibitory nerve-centres which have been surmised to exist; there is, certainly, no paralysis of inhibitory nerve-centres connected with the auricles, and it would be surely pushing ingenuity to a dangerous extent to speculate upon the existence of a special set of inhibitory centres for the ventricular portions of the heart, which are paralyzed by vanadium and which are quite independent of other inhibitory centres for the auricle, over which vanadium has no action! If there were better grounds for the hypothesis of the existence of inhibitory centres in the heart than the fact that the action of one or two interesting cardiac poisons cannot be in any way explained without introducing such centres into our scheme of cardiac innervation, we might as an alternative speculation to the first advance a second—that possibly vanadium impairs the conductivity of the nerve-fibres which bring into communication the inhibitory and motor ganglia of the ventricular portion of the heart; but to speculate in this way appears to us quite puerile.

From the *Journ. of Anat. and Phys.*, Vol. XI.]

ON THE POISONOUS ACTIVITY OF VANADIUM IN ORTHO-, META-, AND PYRO-VANADIC ACIDS.

By LEOPOLD LARMUTH, *Platt Physiological Scholar, Owens College.*

CERTAIN observations which were made in the Laboratory of Owens College at the time when Priestley was investigating the physiological action of vanadium, led that observer and Dr Gamgee to think it possible that the poisonous activity of vanadium might differ in different nearly related compounds —that, probably, the same amount of vanadium would possess a greater poisonous intensity if existing as a pyro-vanadate, or meta-vanadate, than as an ortho-vanadate. To test the accuracy of this surmise, I made, at the request of Dr Gamgee, some experiments which, though few in number, appeared to point decidedly to the conclusion that a given quantity of vanadium is more poisonous as sodium pyro-vanadate, than sodium meta-vanadate, and still more so than as ortho-vanadate. The experiments would probably be too few to entitle one to draw important conclusions from them, had they not been confirmed by the much more extended research on the sodium salts of the exactly corresponding phosphoric acids—a research which has demonstrated that, whilst ortho-phosphates are inert bodies, meta- and pyro-phosphates, and especially the latter, are possessed of considerable activity. I quote from my note-book four sets of experiments which clearly shew that in the case of frogs, ortho-vanadic acid is a less poisonous substance than meta- and pyro-vanadic acids, and in the case of rats, ortho- is less poisonous than pyro-vanadic acid.

In these experiments three standard solutions were employed, prepared by Mr Taylor, Demonstrator in Metallurgy in Owens College, under the superintendence of Professor Roscoe, viz.:

1. A solution of Pyro-vanadate of Sodium,

$$Na_4V_2O_7.$$

2. A solution of Meta-vanadate of Sodium, $NaVO_3$.

3. A solution of Ortho-vanadate of Sodium, Na_3VO_4.

These solutions all contained 5 p.c. of V_2O_5. In addition we were supplied with some solid ortho-vanadate of sodium, to be weighed out and dissolved immediately before being used; the ortho-vanadate is sufficiently unstable to render it advisable that this should be done in some experiments.

EXPERIMENTS I. II. and III. Three frogs designated α, β and γ were accurately weighed, and then 1 cubic centimetre of solutions of the three sodium vanadates were injected under the skin.

α (META-VANADATE).
RANA TEMPORARIA.
Weight 33·57 grms.
1 cc. of Standard Solution of Na VO_3 injected.

In 4 minutes mouth gapes widely and frog makes extraordinary movements as if of retching.

In 10 minutes extends hind legs convulsively.

23 minutes. Lower jaw is drooping. Otherwise appears normal.

55 m. Much as before. Lower jaw still drooping. Movements sluggish and uncertain.

60 m. Lies extended.

65 m. When legs dipped in dilute acid, no reflex movements are induced.

95 m. Upon exposing heart it is found to have stopped beating. On exciting the ventricle mechanically a contraction occurs.

100 m. Heart begins to beat frequently with moderate vigour.

110 m. Heart beating languidly.

125 m. Heart has ceased to beat. On pinching it no contraction.

β (PYRO-VANADATE).
RANA TEMPORARIA.
Weight 31·21 grms.
1 cc. of Solution of $Na_4V_2O_7$ injected.

Immediately after injection appears much excited, leaping about under the bell-jar.

In 9 minutes floor of mouth seems to be bellied downwards.

14 m. Quiet; moves when touched; executes spontaneous movements.

22 m. Sprawls; leaps sprawlingly.

23 m. Lower jaw droops, *i.e.* mouth gapes. Clonic spasms of both hinder extremities.

24 m. Complete paralysis.

28 m. Reflex action abolished.

33 m. Heart exposed, contraction of auricles only; ventricle distended with blood.

38 m. Heart contracts.

43 m. Heart greatly distended.

73 m. Very feeble and irregular beats of heart.

γ (ORTHO-VANADATE).
RANA TEMPORARIA.
Weight 22·26 grms.
1 cc. of Solution of Na_3VO_4 injected.

27 minutes after. Frog seems not perceptibly affected.

70 m. Still quite normal.

130 m. Appears sluggish.

145 m. Sprawling. Leg not drawn up when pinched. When dipped in same dilute H_2SO_4 as α and β vigorous reflex movements.

160 m. Reflex action diminished but not abolished.

170 m. Legs no longer drawn out of acid. Heart exposed; found gorged with blood and beating slowly and irregularly.

EXPERIMENTS IV. V. and VI. Again three active, healthy, frogs were weighed and had injected under their skin quantities of the three salts corresponding in each case to the same quantity of V_2O_5 viz. ·05 grms.

α (META-VANADATE).

R. T. Weight 31·58 grms.
1 cc. of Standard Solution of Na VO_3.

In 18 minutes movements are sluggish. Jaw droops.

27 m. Lies quietly prone. Respirations have ceased. No paralysis of limbs.

36 m. Lower jaw droops. Incipient paralysis of limbs.

37 m. Slight spontaneous movements.

42 m. Cornea quite sensitive. Legs are drawn up sluggishly after being extended. Lies sprawling still.

106 m. after. Reflex action not abolished.

β (PYRO-VANADATE).

R. T. Weight 31·08 grms.
1 cc. of Standard Solution of $Na_4V_2O_7$.

20 minutes. Lies on belly; respiration has ceased. Jaw not drooping.

23 m. Moves in an imperfect, cramped manner.

27 m. Incipient paralysis of limbs.

34 m. Legs lie sprawling.

42 m. Reflex movements on pinching toes.

97 m. Completely paralyzed; no reflex movements on pinching.

132 m. When immersed in acid, legs sluggishly drawn out.

192 m. Heart exposed, auricles beating slowly; ventricle tightly contracted.

γ (ORTHO-VANADATE).

R. T. Weight 31·94 grms.
1 cc. Solution of Na_3VO_4 (Recently made).

26 minutes. Perfectly normal.

56 m. Perfectly normal.

71 m. Somewhat sluggish.

96 m. Lower jaw droops, leaps when touched.

127 m. Moves sprawlingly and falls on its back.

176 m. When feet dipped in acid, not withdrawn.

206 m. Heart still beating, though very feebly.

EXPERIMENTS VII. and VIII. Two white rats of as nearly as possible the same weight were chosen; under the skin of one was injected a recently-prepared solution of ortho-vanadate; under that of the other a solution of pyro-vanadate containing an equivalent quantity of V_2O_5.

RAT α.

Ortho-vanadate of Sodium.
Weight of Rat 208 grammes.

March 21, 1876.

3 h. 5 m. P.M. Injected 0·5 cc. of a solution of ortho-vanadate containing V equal to 0·025 of V_2O_5 injected under the skin.

3.10. Seems perfectly normal.

3.25. Still quite unaffected.

4.50. Perfectly normal. Is moving about actively.

March 22.

11 A.M. Appears rather sluggish; otherwise normal. Eats and drinks. Has no diarrhœa.

2.10. Animal now suffering from diarrhœa. Fæces very fluid and contain much mucus.

March 23.

Found dead this morning.

RAT β.

Pyro-vanadate of Sodium.
Weight of Rat 220 grammes.

March 21, 1876.

3 h. 11 m. P.M. Injected 0·5 cc. of standard solution of $Na_4V_2O_7$, containing V equal to 0·025 of V_2O_5.

3.20. Very quiet. Disinclined to move. Respiration gasping.

3.45. Seems drowsy, moving sluggishly.

3.50. Lies on the side or on the belly, with legs outstretched.

4.15. Still lying on side; is drowsy but moves when touched. Has diarrhœa. Pulpy fæces mixed with mucus.

4.30. When touched, moves about unsteadily and uneasily.

March 22.

In the morning found very sluggish. Great lachrymation. Respirations very laboured.

At 3.15 was found dead.

EXPERIMENTS IX. and X. Again two white rats experimented upon. Plan of experiments same as before; the dose of vanadium increased.

RAT *a*.
Ortho-vanadate of Sodium.
March 23, 1876.
Weight of Rat 158 grammes.

At 12 h. 45 m. P.M. Injected 0·1 grm. of Na_3VO_4 dissolved in 1 cc. of water (=0·05 grm. of V_2O_5).

1.35. Perfectly normal.

4.40. Rather sluggish.

March 24.

9.30. Is very sluggish. Has characteristic lachrymation and diarrhœa. Will not eat.

12.0. Has not moved since last report.

3.0. Is obviously dying.

4.30. Quite dead.

RAT *β*.
Pyro-vanadate of Sodium.
March 23, 1876.
Weight of Rat 143 grammes.

At 12 h. 20 m. P.M. Injected 1 cc. of standard solution of $Na_4V_2O_7$ (containing V=0 05 grm. of V_2O_5).

12.40. Sluggish; respiration jerky and slow.

1.30. Lies on its side, disinclined to move.

1.40. Noticed to have diarrhœa; fæces green, pulpy and contain much mucus.

2.5. In a very drowsy, sluggish state; respiration gasping and uneasy.

4.20. Lying on its side; motionless when touched. Respiration very difficult and slow.

March 24.

9.20 A.M. Found dead.

These four complete sets of experiments demonstrate in a very conclusive manner the fact which we have ascertained by many other experiments, that the poisonous activity of ortho-vanadate of sodium is much less than that of the pyro- or meta-vanadates of the same base.

Although the poisonous activity of vanadium appears to differ in these compounds, their fundamental mode of action is the same; in all its compounds vanadium appears to exert its chief action on the medulla oblongata and spinal cord, rapidly impairing the action of the various centres situated in the former, whilst it interferes in the most marked manner with the reflex action of the latter; in all its compounds it retains its actions as an irritant of the alimentary mucous membrane, and as an agent exerting a definite poisonous action upon the intrinsic nervous mechanism of the heart.

Any speculations as to the cause of the difference of activity of vanadium in the various vanadic acids will be most suitably discussed in relation with the new facts which have been recently discovered in this Laboratory, as to the radical differences in the action of ortho-, pyro-, and meta-phosphoric acids.

From the *Journ. of Anat. and Phys.*, Vol. XI.]

ON THE DIFFERENCE IN THE POISONOUS ACTIVITY OF PHOSPHORUS IN ORTHO-, META- AND PYRO-PHOSPHORIC ACIDS.

By Professor Arthur Gamgee, M.D., F.R.S., John Priestley, *Assistant Lecturer in Physiology and Histology in Owens College*, and Leopold Larmuth, *Platt Physiological Scholar, Owens College.*

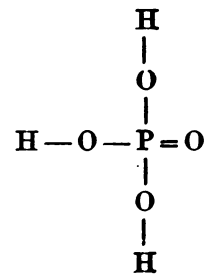
When experiment had shewn that vanadium exerts a different poisonous intensity according as it exists in ortho-, meta- and pyro-vanadic acids, it occurred to us that it would be of great interest to determine whether any similar difference would be manifested by the much better known corresponding phosphoric acids.

Phosphorus pentoxide (or, as it used to be called, anhydrous phosphoric acid) may be made to combine with the elements of water and to yield three most interesting acids, which used formerly to be represented as three hydrates of phosphoric anhydride, and which have, since the researches of Graham made them known to us, been distinguished by the names of ortho-, pyro- and meta-phosphoric acids.

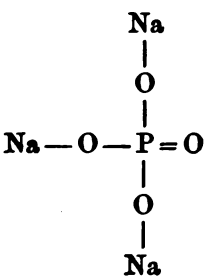
Ortho-, common, or tribasic phosphoric acid used formerly to be known by the rational formula $3HO.PO_5$, which represented it as a compound of PO_5 with three molecules of water; making use of the higher atomic weights which we now universally employ, that formula becomes $3H_2O.P_2O_5$. The fact that ortho-phosphoric acid may be obtained by a direct combination of P_2O_5 and $3H_2O$ does not however warrant the assumption that ortho-phosphoric acid is a compound in which water is linked to P_2O_5; indeed that assumption is disproved by a variety of considerations, and we now write the formula of ortho-phosphoric acid H_3PO_4, which merely indicates that it is an acid which possesses three atoms of H replaceable by three atoms of a

monatomic metal. We may represent the constitution of ortho-phosphoric acid by the formula $(HO)_3PO$, by which we indicate that ortho-phosphoric acid is a compound of the oxygenated radical PO with three atoms of hydroxyl, which may be replaced by one, two, or three atoms of a univalent radical such as NaO.

The following graphic formulæ represent the structure of ortho-phosphoric acid according to this view, and that of normal sodium ortho-phosphate, which is of interest to us as having been used in our research:



$(OH)_3PO$ or H_3PO_4

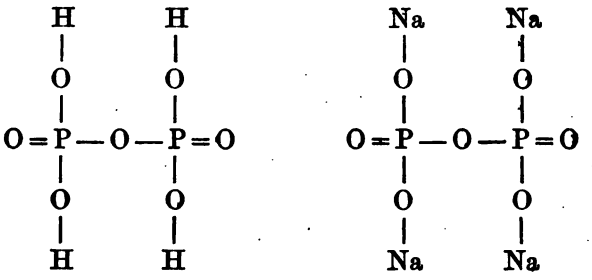


$(NaO)_3PO$ or Na_3PO_4

From ortho-phosphoric acid, by the aid of heat, we can obtain pyro-phosphoric acid, which used to be represented by the formula $2HO.PO_5$ (*i.e.* with the present atomic weights $2H_2O.P_2O_5$), and by the still further application of heat meta-phosphoric or glacial phosphoric acid is obtained.

According to the old view pyro-phosphoric acid was a compound of two molecules of water with one of P_2O_5 and was a dibasic acid. This view of its constitution is certainly incorrect. Pyro-phosphoric acid is a tetrabasic acid, represented by the empirical formula $H_4P_2O_7$, and which may be represented by the constitutional formula $P_2O_3(HO)_4$.

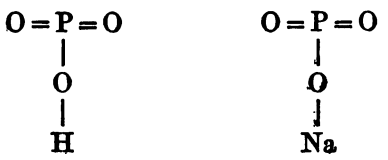
The following graphic formulæ represent the constitution of pyro-phosphoric acid and normal sodium pyro-phosphate:



$H_4P_2O_7$ or $P_2O_3(OH)_4$ $Na_4P_2O_7$ or $P_2O_3(NaO)_4$

Meta-phosphoric acid used to be represented by the formula $HO.PO_3(H_2O.P_2O_5)$, indicating the presence in it of a molecule of water and a molecule of phosphoric anhydride. We now represent it by the empirical formula HPO_3; thus whilst H_2O and P_2O_5 may be obtained on heating the acid, water is not contained in the molecule of the acid, of which two molecules are required in order to furnish one molecule of H_2O.

Meta-phosphoric acid may be represented by the rational formula $PO_2(OH)$, and the graphic formulæ of the acid and of its normal sodium salt may be exhibited thus:



$PO_2(OH)$ $PO_2(ONa)$

Meta-phosphoric acid. Sodium meta-phosphate.

It would naturally be out of place here to describe the methods of preparation, the properties, or the reactions of the three phosphoric acids; the few remarks which we have made on their constitution are to remind our readers of the changes which have occurred in our views of the relation of these compounds, which although genetically related must be looked upon as three distinct phosphorus compounds, in which, in spite of

the fact that they can all be resolved into phosphoric anhydride and water, we probably have three separate oxidized radicals, of different structure. After describing our experiments we shall add some theoretical considerations to try and establish some relation between the constitution and physiological action of the phosphorus compounds under examination.

Historical details. Of the three compounds of phosphorus which interest us only one has hitherto been examined in its relations to the animal economy, viz. ortho-phosphoric acid, and it has been found to have the action of other strong mineral acids when administered uncombined and in a concentrated state[1].

We know of no physiological experiments performed with any of the salts of ortho-phosphoric acid. One of these, disodium hydric phosphate, is officinal, and is used in medicine. The experience of physicians has shewn that this salt is destitute of any active physiological action[2]; when administered in large doses, as from 15 to 30 grammes, it acts as a mild purgative; the mildness of its action and a belief in its exerting a special action on the liver and pancreas[3] has caused it to be used of late years as a mild laxative for children.

Plan of the present research. In investigating the special physiological action of any poisonous acid it appears essential, in the first place, that a compound of the acid with an inactive metallic radical should be selected; for, whilst all facts tell us that the specific action of a poisonous acid is retained in such a compound, we know that in virtue of its mere uncombined state any acid will exert such an immediate action upon the physical structure and even the chemical constitution of the solids and liquids of the body as to mask any special physiological action which the acid may possess. Leaving aside the case where acids are introduced into the body in such large quantities that they exert a corrosive or solvent action on the parts with which they come in contact, we know that if an acid or a salt of acid reaction be introduced into the blood in a quantity at all greater than suffices to neutralize the feeble alkalinity of that fluid, we

[1] Hermann, *Lehrbuch der experimentellen Toxicologie.* S. 158.
[2] Nothnagel, *Handbuch der Arzneimittellehre.* Zweite Auflage. S. 213.
[3] Stephenson, *Edinburgh Med. Journal*, 1867, Vol. XIII. p. 336.

have at once an energetic decomposition of the blood-colouring matter, which splits up into hæmatin and a proteid body, besides precipitation of proteids contained in the plasma which are held in solution by the alkalis contained in that fluid. When such changes are induced it is needless to say that we may seek in vain for the specific results of the physiological action of the substance which has led to their occurrence.

In order to obviate any effects which might depend upon mere acidity and to make our experiments comparable, we usually experimented with the solutions of pure trisodic ortho-phosphate, tetrasodic pyro-phosphate and sodium meta-phosphate, in most of our experiments making use of standard solutions which contained the same amount of phosphorus, calculated as P_2O_5.

Our experiments were performed on frogs, rabbits, and dogs, and the drugs investigated were generally introduced into the system either by injecting their solutions subcutaneously or into the veins. They will be divided into three series; only those experiments are quoted which are required to bring out prominently the fact of the great difference in poisonous intensity which exists between ortho-, meta- and pyro-phosphoric acids, all the experiments which specially elucidate the action of pyro-phosphoric acid as a poison of the circulation being reserved for a separate communication.

Experiments on Sodium Ortho-Phosphate.

Exp. I. A solution of pure crystallized disodium hydric phosphate ($Na_2HPO_4+12H_2O$) made, containing 2·5 per cent of P_2O_5.

H. M.

1 . 55. Injected 1 cc. of this solution under the skin of a small frog weighing 14·29 grammes.

After the injection the frog appears quite active and leaps away.

H. M.

2 . 10. Frog is quite lively, leaping about under the bell-jar.

2 . 15. No perceptible effects; frog appears quite lively.

The frog was observed at intervals till 5h. 10m., no poisonous action being noticed; it was then placed in the trough, and the following morning it was found in a perfectly normal condition.

Exp. II. (1 | 3 | 76.)

H. M.

12 . 13. Injected 2 cc. of the same standard solution of sodium

ortho-phosphate under the skin of a frog weighing 20·655 grammes; after the injection the frog leaps away actively.

12 . 55. The frog appears perfectly normal. After this the frog was watched carefully until 6 p.m., when it was placed in the trough; on the following morning it was found to be perfectly normal.

Exp. III. (12 | 3 | 76.) A rabbit weighing 1838 grammes had its left carotid connected with the kymographion, and three separate quantities of solution of ortho-phosphate of sodium were injected into the right jugular vein.

The solution contained 2·5 per cent. of P_2O_5 as tri-sodium ortho-phosphate, and the quantity injected each time was 2 cc., so that in all 0·15 grm. of P_2O_5 as ortho-phosphate was injected. Between the 1st and 2nd doses the interval which elapsed was 8 minutes and 5 seconds, between the 2nd and 3rd 26 minutes and 40 seconds. Throughout the whole experiment no appreciable change occurred in blood-pressure, in number or character of heart-beats.

Without quoting the actual notes of the experiment in detail, we may illustrate the statement by giving the arterial pressure and heart-rate for 10 seconds before the 1st injection of the drug, after the 2nd and 3rd.

H.	M.	S.			
1	29	0.	Before 1st injn.	arterial pressure 85 mm.	P. 52 in 10 secs.
1	37	35.	After 2nd injection	ditto 85 mm.	P. 52 in 10 secs.
2	4	20.	After 3rd injection	ditto 83 mm.	P. 52 in 10 secs.

This rabbit was released and appeared perfectly normal after the experiment. It was, as an exception to our usual laboratory rule, allowed to live, in order that its state might be watched. It continued perfectly normal, and on the 20th March, being in perfectly good health, it was subjected to the action of sodium pyro-phosphate.

Exp. IV. A vigorous rabbit, the weight of which was unfortunately not ascertained, was experimented upon as the one in Exp. III. In this case 12 injections of the same solution of sodium ortho-phosphate, each of 1·75 cc., were made into the jugular vein, so that in all 21 cubic centimetres of a solution of ortho-phosphate containing 0·25 per cent. of P_2O_5 were introduced into the circulation, but, as will be seen from the following data, there was no perceptible effect produced either upon blood-pressure or heart-beats.

Time.				Blood Press.	Plse. in 10 secs.
H.	M.	S.			
12	57	15.	Before 1st injection.....	134	48
1	12	45.	After 4th injection	128	38
1	24	30.	After 8th injection	138	40
1	33	0.	During 12th injection.....	124	44

No phenomena of any kind were observed to be produced by the injection into the blood of this rabbit of sodium ortho-phosphate containing 0·525 grm. of P_2O_5.

The experiments which have been narrated shewed that sodium ortho-phosphate was apparently an inert substance, contrasting, as will be seen, in a very marked manner with sodium pyro-phosphate.

For reasons which will appear obvious in the sequel, the following experiments were performed:

Exp. V. (10 | 3 | 76.)

H.	M.	
3	0.	Heart of Rana temporaria prepared for Coates' experiment. Connection made with serum reservoir and gauge. Reddish and fresh rabbit's serum used.
3	20.	Normal tracing taken. Heart is beating vigorously 6 times in 10 seconds.
3	30.	A second tracing taken; exactly same as first. Serum now mixed with 1-24th of its volume of a standard solution of Na_3PO_4 containing 5 per cent. of P_2O_5.
3	35.	Heart beats with great vigour and perfect regularity.
3	50.	Tracing again taken. Heart beats very vigorously, only about 3 times in 10 seconds.
4	30.	Heart still beating vigorously 4 times in 10 seconds.
5	50.	Heart still beating vigorously 4 times in 10 seconds.

Exp VI. (14 | 3 | 76.) Rana temporaria prepared for Coates' experiment.

H.	M.	
1	10.	Tracing taken. Heart beating normally 5—6 times in 10 seconds.
2	10.	Another normal tracing taken. Heart still beats 5—6 times in 10 seconds.
2	15.	The pure serum replaced by a mixture of 1 volume of standard solution of Na_3PO_4 and 9 volumes of reddish rabbit's serum.
2	20.	Ventricle contracting imperfectly and irregularly. A tracing taken which is but a wavy line.
2	30.	Heart beating more perfectly than before, still slowly.
2	40.	Ventricle now again contracts with very great vigour, and contraction lasts long. About 2 contractions in 10 seconds.
3	30.	Ventricle still contracting energetically, but very slowly and somewhat irregularly.

Experiments with Sodium Meta-phosphate.

In these experiments a solution containing $NaPO_3$ was made. The P calculated as P_2O_5 amounted to 5 per cent. It therefore

contained in an equal volume twice as much P as the solution of ortho-phosphate employed in Experiments 1 to 6.

Exp. VII. (13 | 3 | 76.)

H. M.

3 . 30. A vigorous specimen of Rana temporaria weighing 33·72 grammes had 1 cubic centimetre of the standard solution of sodium meta-phosphate injected under the skin. The frog leaped away vigorously after the injection.

3 . 35. Frog appears to be in a perfectly normal condition.

3 . 40. No perceptible change in the frog.

3 . 50. In same state as before.

4 . 40. Is sluggish: does not move at once when touched. Partial paralysis of hind limbs.

5 . 50. Very sluggish. Lies on belly with hind limbs extended. Reflex action is impaired but not abolished.

The frog was then placed upon moistened filter paper under an inverted funnel. On the morning of the 14th the frog was found to have apparently recovered.

Exp. VIII. (12 | 3 | 76.) A rabbit weighing 1794 grammes.

H. M.

4 . 0. Injected 1 cc. of standard solution of sodium meta-phosphate into left external jugular vein. No change in the animal's condition resulted.

4 . 52. Injected 1 cc. more of solution. After it appears absolutely normal.

5 . 20. Injected 2 cc. of solution (= 0·10 grm. of P_2O_5). No change.

6 . 0. Appears in perfect health. Is eating. The wound was stitched up and the animal recovered.

Exp. IX. (20 | 3 | 76.) Rabbit weighing 1678 grammes.

H. M.

3 . 40. The rabbit being quite well and its temperature 39·4°, 5 cc. of standard solution of sodium meta-phosphate (containing P corresponding to 0·25 grm. of P_2O_5) were injected under the skin. No symptoms were noticed.

The following day, 21st March, 1876, at 10 a.m., the animal seemed normal. Temp. 39·2°. Respirations appear slow.

By an accident one of this rabbit's legs was broken and it was killed.

Sectio Cadaveris. Liver greyish throughout, friable; not decidedly, but doubtfully fatty. Kidney mottled extensively with white; medullary portion congested; cortical portion swollen; renal epithelium somewhat cloudy. Bladder filled with brown thick urine, which was albuminous.

Exp. X. (14 | 3 | 76.) Rana temporaria prepared for Coates' experiment. Fed with reddish rabbit's serum.

H. M.

3 . 50. Normal tracing taken. Heart is beating regularly and vigorously 5—6 times in 10 seconds. Tracing taken.

4 . 30. Heart beating still regularly. Another tracing taken and found not to differ sensibly from the last.

Pure serum now replaced by a mixture of 1 volume of standard solution of meta-phosphate and 25 volumes of serum.

H. M.

4 . 32. Ventricle hardly contracting. Is distended; cannot get a tracing. Auricles contracting.

4 . 45. In same state as before. Auricles contracting imperfectly 10 times in 30 seconds. Direct mechanical excitation does not cause the ventricle to contract.

4 . 48. Auricle contracting 11 times in 30 seconds.

5 . 15. Ventricle as before. No contraction on excitation. Auricles contracting very feebly 11 times in 30 seconds.

Experiments with Sodium Pyro-phosphate.

In this series of experiments solutions of pure sodium pyro-phosphate were prepared either by dissolving the crystallized salt, $Na_4P_2O_7 + 12H_2O$, or the anhydrous salt obtained by igniting the above.

Exp. XI. (29 | 2 | 76.)

H. M.

12 . 20. An active English frog weighing 16·4592 grms. had 1 cub. cent. of a standard solution of sodium pyro-phosphate injected under the skin of the back. The solution of pyro-phosphate corresponded to 2 per cent. of P_2O_5.

12 . 40. Appears quite active, leaping about under the large funnel by which it is covered.

12 . 50. Struggles as if attempting to leap, but unable.

1 . 2 . 5. Lies with limbs extended. No movement on pinching toes.

1 . 25. Frog appears dead. Limbs are perfectly flaccid and motionless. No reflex action on exciting the skin.

1 . 27. Left sciatic exposed. Excited by weak induction shocks of Du Bois Reymond's induction coil. With secondary coil at 28 centimetres from primary, muscles contract well.

1 . 33. Upon exposing the heart it is seen to be engorged with venous blood and beating regularly 15 times in 30 seconds.

1 . 55. Upon galvanizing the left sciatic muscular contraction still takes place.

2 . 15. Movements of leg still occur on exciting sciatic.

Exp. XII. (29 | 2 | 76.)

H. M.

2 . 7. Injected 2 cc. of the same solution of pyro-phosphate of sodium under the skin of a healthy R. temporaria weighing 22·32 grammes.

2 . 30. Frog sprawls; cannot support itself on its anterior extremities.

2 . 35. Lies passive and flat. When hind limbs are extended does not draw them forwards. Still possesses apparently some slight power of voluntarily moving its body. There is in fact a state of paresis, if not of paralysis.

3 . 10. Frog perfectly flaccid. Reflex action found to be completely abolished when limbs are dipped in dilute H_2SO_4.

3 . 15. Upon exposing left sciatic and exciting by means of weak induction shocks (secondary coil of Du Bois Reymond's apparatus at 28) twitching of the legs occurs.

4 . 25. Heart exposed and found to be beating feebly but regularly 14 times in 30 seconds.

Exp. XIII. (2 | 3 | 76.)

H. M.

9 . 56. A very active R. temporaria weighing 39·49 grms. had 1 cc. of the same solution of $Na_4P_2O_7$ injected under the skin.

10 . 15. Frog very inactive.

10 . 20. Frog sprawls. On pinching hind legs they are fully drawn up.

10 . 40. Frog in a very sluggish state, still after posterior extremities have been extended they are slowly drawn up.

10 . 50. Frog lies perfectly flaccid.

11 . 0. In same state as before. No reflex movements when toes are pinched.

11 . 30. Frog lies perfectly flaccid. Reflex action tested by dipping legs into dilute H_2SO_4, and found to be abolished.

11 . 35. Heart exposed. Is engorged with very venous blood and beats regularly 17 times in 30 seconds.

11 . 50. Heart beating very slowly and imperfectly.

12 . 15. Heart in a very distended state: scarcely pulsating.

Exp. XIV. In this experiment a rabbit weighing 2535 grammes was employed. 2·5 cc. of the standard solution of sodium pyro-phosphate, as used in the last experiments, was mixed with 5 cc. of sheep's serum.

H. M.

4 . 1. 2 cc. of this mixture injected into the external jugular vein.

4 . 5. Injection completed. No convulsions or movements.

4 . 20. Appears normal.

5 . 0. Seems quite normal.

5 . 2. Injection of other 2 cc. commenced.

5 . 5. Injection completed. No convulsions. Appears drowsy (?).

5 . 33. Injected nearly, but not quite, 2 cc.
5 . 35. Stretching convulsions. Paralysis of hind limbs.
5 . 38. Severe stretching convulsions. Eyes insensitive. Gasping respiration.
5 . 40. Tremors of lips.
5 . 50. *Sectio cadaveris.* Right heart is distended; auricles are beating.

Exp. XV. Rabbit weighing 2265 grammes.

H. M.
12 . 16. Respirations 20 in 10 seconds.
12 . 51. Injected 2·5 cc. of same solution of sodium pyro-phosphate (this quantity of solution contains P = ·05 grm. of P_2O_5) into the external jugular vein. Struggles; when released moves about normally. Respirations 11—13 in 10 secs.
1 . 9. Seems normal; if anything is rather drowsy.
1 . 15. Respirations 10 in 10 seconds. Heart beats 40—44 in 10 seconds.
1 . 38. Injection of 5 cc. of the solution (=·10 grm. of P_2O_5).
1 . 39. Most severe convulsions, opisthotonos; clonic, stretching convulsions. Cornea insensitive. Respiration rapid and powerful.
1 . 41. Cornea quite sensitive again. Complete paralysis of posterior but not of anterior extremities. Respirations 36, 34, 33, and 34 in 10 seconds. Hind limbs now lax and quite paralyzed. No reflex action follows pinching any portion of skin, but movements of eyelids follow irritation of the cornea.
1 . 46. Heart beats 40 times in 10 seconds. On touching its fore-legs the rabbit moves its eyelids but not its limbs. Paralysis of whole body except head.
1 . 49. No alteration of eye on pinching the legs. Attempts to move in a wriggling manner. Sharp slight opisthotonic movements. Opisthotonos. Cessation of respiration. Pupils dilating. Stoppage of heart.
1 . 52. Is quite dead.
1 . 57. *Sectio cadaveris.* Slight movements of heart, the cavities of which, especially the right, are gorged with blood. Vermicular movements of intestines are proceeding actively. Intestinal vessels are much injected with blood.

Exp. XVI. (15 | 3 | 76). Rabbit weighing 1595 grammes.

H. M.
1 . 55 p.m. 12·5 cc. of a solution of sodium pyro-phosphate solution (containing P=2 per cent. of P_2O_5) diluted with 8 cc. of water were injected under the skin of the left side.
3 . 30. The rabbit is lying down and appears normal.
4 . 25. Crouches or lies as if sleepy; otherwise is normal.

March 16.

9 . 30a.m. Rabbit appears weak and ill; sniffles in breathing. Can walk, but is weak. Respiration 5—6 in 10 seconds, deep.
2 . 47. Temperature in rectum 35·6° C.
5 . 30. The same state as before.
9 . 37. Respiration 5–6 in 10 seconds.
10 . 45. Condition remains unaltered. Drinks greedily.

March 17.

11 . 30 a.m. Temperature in rectum 34·1° C. Lies on its side unable to stand. Bladder emptied by pressing abdomen. 28 cc. of urine were obtained; reaction acid; contains a large quantity of albumen; contains a doubtful trace of bile-colouring matter and no sugar. Chlorides appear deficient.
1 . 28. Respirations 10 in 10 seconds. Cannot stand.
1 . 38. Found dead.

Sectio cadaveris. On dissecting the skin from the middle line of the abdomen the cellular tissue is found to be œdematous, so that large quantities of fluid trickle away. Auricles and ventricles of heart have ceased to beat. Both sides of the heart contain blood, which coagulates on exposure. Lungs normal. No appearance of peritonitis. Intestinal peristalsis still going on. Stomach contains a small quantity of food. On opening it a few doubtful punctiform extravasations were seen. Duodenum contained much greenish gelatinous mucus. Its upper part presents injection of the mucous membrane. Small intestine appears injected throughout its entire length. Liver appears normal. Right kidney is fatty; left not markedly so. Bladder contains some urine.

Exp. XVII. (20 | 3 | 76.) Rabbit weighing 1813 grms.

H. M.

1 . 0 p.m. Temperature in rectum 39·8° C. Injected 6·25 cc. of standard solution of $Na_4P_2O_7$ below the skin (the P in this quantity is equal to 0·125 grm. of P_2O_5).
1 . 15. Seems slightly uneasy.
5 . 30. Lies quiet.

March 21.

10 . 0 a.m. Appears to be in a normal condition.
11 . 45. Temperature in rectum 38·5° C.
5 . 40. Has eaten well, and seems in good health. T. 38·4°. Again injected 6·5 cc. of same solution.

March 22.

9 , 30. Seems normal; perhaps a little quieter than usual.
1 . 25. Appears normal. T. 39° C. Respirations 17 in 10 seconds.
4 . 0. Temperature 39° C.
4 . 50. Injected 6·5 cc. of same solution under skin.

March 23.

8 . 30 p.m. Temp. 38·6°. Respiration 10 in 10 seconds and irregular. Apparently some cellulitis where injections have been practised.

8 . 53. Injection 6·25 cc. of same solution. The rabbit is losing flesh; it eats, but not greedily.

March 24. Seems very quiet; has eaten all its food.

12 . 45 p.m. Respiration 7 in 10 seconds and very shallow. Temp. in rectum 38·1° C.

March 25.

1 . 0 p.m. Temperature 39·2° C. Is very thin. Has had diarrhœa. Drinks greedily.

1 . 30. Respirations 9 in 10 seconds, jerky and irregular.

March 27.

10 . 0 a.m. Seems much brighter, eats and drinks greedily. Moves about with alacrity, and evinces interest in what transpires around it. Respiration 9—10 in 10 secs. Temp. 38·8° C.

4 . 30. Repeated injection of 6·5 cc. of standard solution.

March 28. Lies on its side. Moves fore-legs normally.

9 . 30 a.m. Cannot stand up. Anterior half of body appears hyperæsthetic. Respiration 9 in 10 seconds. Temp. 37° C.

12 . 0. Still lies on its side. Nibbles its food eagerly.

5 . 40. Temperature in rectum 37·1° C. Fæces are light brown but firm.

March 29. Noon. Died.

Sectio cadaveris. Extensive effusion into the connective tissue, which in parts was indurated. This was not accompanied by congestion and no tendency to the formation of pus.

Stomach quite empty of solid food, but contains a bright green fluid (!). Exhibits on its mucous membrane a few brown hæmorrhagic spots and patches. Small intestine contains yellow contents, viscid and turbid. On serous surface of intestine a few slight blood extravasations are noticed. Peyers' patches are quite normal. Vermiform appendage quite normal. Large intestine normal. Kidneys large and white; much congested, very friable. Medullary portion of kidney swollen. 'Grenzschicht' congested. Bladder contained thick and muddy urine with an abundant sediment containing a large number of very fatty cast mixed with phosphates. Liver dark-coloured, but fatty. Heart somewhat fatty. Clear coagulum in auricles. Lungs normal.

Exp. XVIII. Rabbit weighing 1835 grms.

March 14, 1876.

3 . 45. Injected under the skin a solution of 3·14 grms. of anhydrous $Na_4P_2O_7$.

3 . 55. Very excited. Tendency to fall over on its side.
4 . 0. Respiration 26 in 10 seconds.
4 . 18. Respirations 14, 15, 16 in 10 seconds.
5 . 0. Respirations 13 and 14 in 10 seconds.
6 . 10. Lies in corner of hutch. Moves with difficulty.

March 15.

8 . 30 a.m. Found dead and quite rigid.
11 . 30. *Sectio cadaveris.* Intense congestion of abdominal muscles and infiltration of subcutaneous connective tissue of the right side of abdomen and back. Mesenteric vessels injected. Stomach presents intense brown patches at the cardiac and back wall, together with a general redness near the œsophageal end. Intestines filled with thin, gruelly contents. Vermiform appendage congested. Spleen normal. Kidneys normal, liver not fatty. Heart much distended on right side. Left ventricle contracted. Lungs not congested. Bladder firmly contracted.

In order to avoid the repetition of experiments, we shall not here quote any experiments with serum poisoned with sodium pyro-phosphate, by Coates' method, although these experiments are needed to allow of a comparison between the experiments of series I, II, and III. As the Coates experiments are quoted in the paper in which we treat of the special action of sodium pyro-phosphate as a poison of the circulation, we shall here only state their results. Sodium pyro-phosphate exerts upon the frog-heart exactly the same action as sodium meta-phosphate, except that it is, if anything, rather more energetic, *i.e.* when 1 volume of a solution containing P corresponding to 2 per cent. of P_2O_5 is mixed with 25 volumes of rabbit's serum, and the mixture is made to circulate through the heart, the ventricle is at once arrested, becoming powerfully contracted, whilst the auricle continues to beat though with great feebleness.

Having stated the main facts of our researches, it will be well that we should point out the general conclusions.

It results from our observations that ortho-phosphoric acid in combination with sodium is a substance which is destitute of any marked physiological activity. When taken into the alimentary canal of man it produces no marked result, save that which appears to follow the injection of other inert neutral alkaline salts. When injected under the skin of frogs, these most susceptible animals remain perfectly unaffected, and no result is observed when large quantities are introduced directly into the veins of rabbits. The only result which may be called a positive result was obtained when serum containing a large quantity of sodium ortho-phosphate was made to circulate

through the frog's heart. It was found that although the heart went on beating, even for hours, the pulsations were slower than normal and altered in character. These changes however are fully accounted for by the amount of the sodium salt present in the serum, and which must in a most marked manner, by diffusion, have initiated physical changes in the frog's heart. The slowing of the heart, with powerful lengthened systoles, is observed by Coates' method when serum which is not quite adapted to the frog's heart (*e.g.* sheep's serum) is used.

With regard to meta-phosphate of sodium, our experiments conclusively shew that it is a poisonous substance, although not by any means as poisonous as sodium pyro-phosphate. It appears to share the action of the latter as a direct poison of the heart.

Pyro-phosphate of sodium is shewn to be a substance of great poisonous activity. Our experiments have clearly demonstrated that in its action on frogs it is more poisonous than sodium ortho-vanadate, having about the same intensity as sodium pyro-vanadate. In rabbits, when introduced into the circulation, it is very poisonous, although its action is certainly not so marked as that of the corresponding vanadium compound.

When we glance at the symptoms induced by sodium pyro-phosphate, we find that it is a poison which induces death without materially affecting the irritability of voluntary muscles or of nerves. It exerts an action on the spinal cord and medulla oblongata, which resembles most closely that of vanadium compounds. Upon the heart too its action is very similar to that of vanadium. Upon the alimentary canal sodium pyro-phosphate has in some cases appeared to exert no marked action. In others it has induced appearances identical with those observed in some cases of phosphorus poisoning. In its effects on the general nutrition the poison has shewn great resemblance to the poisonous element phosphorus which it contains, for in cases where death has been delayed there has been very marked fatty degeneration of the kidneys, of the muscular substance of the heart, with slighter degeneration of the liver.

In the account which we have given of the action of pyro-

phosphoric acid, we have not attempted to state the results of all our researches, much less have we pretended to give a complete account of the physiological action of the body. We must, however, allude to one result which has surprised us, and which we hope to elucidate by fresh experiments. We have never succeeded in producing symptoms of poisoning by sodium pyro-phosphate when we have introduced the substance into the stomach. In dogs the drug has produced vomiting but no further ill effect; rabbits have remained unaffected by it; so striking was this absence of poisonous symptoms that it appeared to us possible that some of the alimentary ferments might cause sodium pyro-phosphate to combine with the elements of water, and convert it into the inert ortho-phosphate; direct experiments, in which salivary, gastric, and pancreatic ferments were digested with pyro-phosphate at the temperature of the body, proved that our surmise was not correct. At present we are inclined to think that the fact of animals not being poisoned when sodium pyro-phosphate is introduced into their alimentary canal is due to the rapid elimination of the drug.

Whilst we are, as at present, so thoroughly in the dark as to the conditions of poisonous activity—for we do not know in virtue of which physical or chemical properties the molecules of a poisonous body interfere with the physical properties or the chemical structure of the elementary tissues and organs, and so lead to those disturbances of function which constitute poisonous action—it may appear premature to speculate on the causes of the inactivity of phosphorus in most of its compounds, an inactivity which demands explanation.

Whilst arsenic, antimony, and vanadium exert their characteristic actions on the alimentary canal, on the nervous system, on general nutrition, almost irrespective of their state of combination, phosphorus fails to impart to many of its compounds any poisonous activity; indeed it can scarcely be said to exert what we may term its elementary action, except when uncombined, and then only when in the condition of yellow phosphorus.

We need not seek for a better example of an inactive phosphorus compound than is furnished by sodium ortho-phosphate, which we have conclusively proved to be physiologically a per-

fectly inert body. Why should phosphorus in Na_3PO_4 be inert, whilst vanadium and arsenic exert their characteristic action with energy in the corresponding arseniate and vanadate?

If the poisonous action of poisonous elements be due to definite chemical operations performed by them in the body, *i.e.* if for its development the elements have to take part in chemical reactions, it is quite conceivable, as indeed Hermann has hinted, that the compounds of arsenic or antimony should be more poisonous than those of phosphorus, for they are much more unstable. We know, for example, with what ease compounds of arsenic and antimony take part in reactions which do not succeed with phosphorus; the action of zinc and sulphuric acid on an antimoniate, an arseniate, and a phosphate, offer a good illustration of this difference. In the two former cases the nascent hydrogen is capable of attacking the Sb and As to form their gaseous hydrides; in the latter the phosphorus is so firmly linked to oxygen that the attack fails. Similarly we may conceive that in the body an ortho-phosphate will escape all fundamental decomposition; its phosphorus will never present itself in any chemical operation except in the condition of a saturated compound.

We do not believe that we are outstepping the limits of justifiable scientific speculation in assuming that a poisonous element will be unable to exert its characteristic *elementary* poisonous properties unless it can itself take part in chemical reactions, and this it will not be able to do if it passes through the body with all its affinities saturated; we do not by this mean to imply that no saturated compound can, in its passage through the body, exert an action unless it be decomposed, for it is probable indeed that the activity of many organic bodies is really due to an action of their undecomposed molecules upon the molecular structure of tissues and organs.

Our contention is that the action of an element itself, say As, V, or Sb, or P, will not be manifested except it enters into reactions which shall for the time leave some of its affinities unsaturated. How can we explain the inactivity of cacodylic acid, which contains about one half of its weight of arsenic, except by supposing that in this saturated compound the arsenic is so securely linked to carbon and oxygen atoms, that in no

reaction of the body does it present affinities to be saturated—that in no reaction does it appear as arsenic? On the other hand, we can easily understand how in the much more complex molecule of cacodyl the affinity which links arsenic to arsenic should be overcome with considerable ease, leaving the unsaturated arsenic atoms to exert their full action upon the elementary organs where the decomposition occurs.

In pyro-phosphoric acid and the pyro-phosphates we have examples of bodies of much greater complexity than the ortho-phosphates, and in which the phosphorus is not fully saturated. We can readily understand that such a body as pyro-phosphoric acid might, either in its integral condition (in virtue of the state of the phosphorus of its molecule) attach itself to other bodies and exert a specific phosphorus action, or that it might in the body undergo decomposition, and at the time of decomposition be in a fit state to enter into chemical reactions.

Similarly in meta-phosphoric acid phosphorus affinities are not as fully satisfied as in ortho-phosphoric acid, and the body is one which would presumably exert a greater action than ortho-phosphoric acid.

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ON THE ACTION OF PYRO-PHOSPHORIC ACID ON THE CIRCULATION.

By PROF. GAMGEE, M.D., F.R.S., JOHN PRIESTLEY, *Assistant Lecturer in Physiology in Owens College*, and LEOPOLD LARMUTH, *Platt Physiological Scholar, Owens College.* (With a Plate.)

WE have already drawn attention to the interesting fact that whilst sodium ortho-phosphate is a substance possessing no activity as a poison, the meta-phosphate is undoubtedly poisonous, and the pyrophosphate still more so. The facts which bear upon the general action of the latter compound have been cited, and we have endeavoured to shew that sodium pyro-phosphate exerts an action which, in so far as the nervous system and the circulation are concerned, is very similar to that of the corrresponding vanadium compound.

As we are very much interested in the discovery of the physiological relations which may exist between the different members of the most interesting group of elements to which both phosphorus and vanadium belong, we determined upon making a somewhat exhaustive examination of the action of sodium pyro-phosphate on the circulation of the blood, so as to be able to compare the facts thus obtained with those yielded by the analogous research already conducted with the vanadium compound.

Our experiments have been performed on rabbits and frogs, the latter animals having been employed in studying the direct action of sodium pyro-phosphate on the heart.

In seven cases we have determined, by means of the kymographion, the changes induced in rabbits when sodium pyro-phosphate is introduced into the circulation. Of these seven perfectly concordant experiments, we have given the notes of five. Three experiments illustrate the effects of the salt on rabbits with spinal cord and vagi intact. One experiment shews the changes which occurred when the vagi had been divided; and another exhibits the effects on a curarized

rabbit, of which the cord had been divided at the atlanto-occipital articulation.

Exp. I. Rabbit, 1755 grm. Dose, 1·65 cc. solution of sodium pyro-phosphate, containing 2 per cent. P_2O_5 injected into vein. Kymograph at carotid.

Time.	Pulse in 10 sec.	B. P.	Remarks.
H. M. S.			
1.18	38	111	Normals. Resp. curves 10 in 10 sec.
1.18.12	39	118	Injection commenced.
1.18.19	39		B. P. begins to fall. Pulse slightly irregular.
1.18.20		108	
1.18.21			Pulse becomes extremely slight and slow, and the B. P. falls lower.
1.18.35		69	
1.18.40			Injection complete; at which time struggles or convulsions sent up the B. P. irregularly, keeping it up until 1h. 18m. 52s., after which the heart seemed to cease and the B. P. fell gradually and steadily. Breathing continued, although the heart never went on again.
1.21.30	none	25	Movements occurred, not altering B. P.
1.22.30	none	25	Pinching the legs caused movements of lips.
1.23	none	25	Slight respiratory movements.
1.24	none	25	Movement on pinching hind leg.
			Dead.

Exp. II. (See Plate IX.) Rabbit, 1665 grm. Dose, 3·2 cc. of solution of pyro-phosphate of soda, containing 2 per cent. P_2O_5 injected into ext. jugular vein.

Time.	Pulse in 10 sec.	B. P.	Remarks.
H. M. S.			
			Kymograph at carotid.
4.20.40	44	124	Normals. Resp. curves 5—6 in 10 sec.
4.21.7	44	124	Injection commenced.
4.21.20	44	124	Resp. curves as before.
4.21.22	44		B. P. begins to fall. Pulse a little irregular.
4.21.30	43	102	B. P. gradually falls. Pulse becomes very irregular.
4.21.35	20	80	Pulse large and slow. B. P. gradually fallen.
4.21.37			Struggles send up B. P. Injection complete.
to	23		Struggles send and keep up B. P. Pulse large,
4.22			slow, and irregular.
4.22	22	90	Pulse becomes very slow, and slight.
4.22.30	none		B. P. falls in a sweep to 40 mm.
4.22.40	none	84	B. P. gradually falls. Convulsions occur, not affecting B. P.

Exp. III. Rabbit, 1775 grms. Dose, $\left.\begin{matrix}2\text{ cc.}\\2\text{ cc.}\end{matrix}\right\}$ of solution of pyrophosphate of soda, containing 2 per cent. P_2O_5 injected into right ext. jugular vein.

Time.	Pulse in 10 secs.	B. P.	Remarks.
H. M. S.			Kymograph at carotid.
4.19.50	49	104	
4.22.55	44	108	Resp. curves 9 in 10 sec.
4.23	44	108	Injection of first dose commenced.
4.23.15	28	106	Pulse begins to get slower and less regular.
4.23.20			B. P. begins to fall.
4.23.25		100	Pulse very large and irregular.
4.23.35	22—10	46	B. P. falls quickly, the heart having become extremely slow.
4.23.40			Very severe struggles, sending up the B. P.
to			Heart simultaneously ceases.
			Struggles continue.
4.24.10			Struggles continue.
	22		Heart recommences.
4.24.20			Convulsions occur, raising the B. P. very much.
4.24.30	18	78	B. P. rising. Pulse very large and irregular.
4.24.55	22	112	B. P. steadily rises. Pulse as before. No struggling.
4.25.40	27	110	B. P. steadier. Pulse getting more regular: B. P. presents several marked variations.
4.25.42			Heart ceases again: no struggles occur, and
4.25.46		60	B. P. falls at once to 60 mm.
4.25.48			Heart beats 20 or 30 times, becoming gradually weaker towards the close of the series, during which the B. P. rises again slightly, but falls again as the pulse becomes weaker.
4.26		38	Convulsions which do not at once or violently affect the B. P.
			During the next minute the B. P. rises and falls very gradually and regularly three or four times,
	24		producing long sweeping curves on the cylinder, varying in height from 30 mm. to 48 mm., during which the heart beats slowly and feebly, but quite regularly,
4.27		48	
4.27.30		82	Convulsions send up the B. P.
4.27.45		88	
4.28			The B. P. irregular but, as a mean, higher.
4.28	47	86	Resp. curves now reappear two or three times for
to	to	to	about 15 sec., disappearing to give place to a
4.30	45	64	straight B. P. line.
			After this the B. P. became quite normal and finally attained a height of 100 mm.
4.41	47	100	Resp. curves well shewn (12 in 10 sec.). Pulse normal.
4.41.5			Injection of second dose commenced.
4.41.15	46	100	Resp. curves well shewn (12 in 10 sec.).
4.41.20	41—42		B. P. begins to fall. Pulse a little irregular and slighter.
4.41.25	20	93	Pulse becomes long and slow: and B. P. begins to fall.
4.41.50	24	62	B. P. gradually fallen. Pulse long (*i.e.* infrequent).
4.42			Opisthotonic convulsions which raise and disturb B. P.
4.43	21	35	B. P. steadily falling. Pulse feeble. Convulsions again follow, with slighter disturbances of B. P. Pulse becomes feebler and feebler.
4.45.30		9	B. P. has fallen steadily. Dead.

EXP. IV. *Division of Vagi.* Rabbit, weight 2657 grms. Injection of solution of sodium pyro-phosphate, containing 2 per cent. P_2O_5, into jugular vein. Carotid connected with kymograph.

Time.	Blood Pressure in mm. mercury.	No. of Respirations in 10 secs.	No. of Heart-beats in 10 secs.	Remarks.
H. M. S.				
4. 0. 0	74	7	40	Normal.
4. 2.52				*Left vagus divided.*
4. 3. 0	92		43	Respiration irregular.
4. 3. 9	122			
4. 3.10	119			
4. 3.12	124			
4. 3.15				*Right vagus divided.*
			43	In next 10 seconds.
4. 3.17	116			
4. 3.20	124			
4. 3.25	139			
4. 3.30	142			
4. 3.35 to 4. 3.40	.....	.....	.....	Struggles.
4. 3.53	148			
4. 4.10	144			
4. 4.20	144	Slow and		
4. 4.45	134	irregular.		
4. 5. 0	132	Generally	42	
4. 5.30	124	2-3 in 10 s.		Pressure varies 12 mm. between
4. 6. 0	120		41	inspiration and expiration.
4. 6.20	124			
4. 7.20	120	2	42	
4. 9. 0	112		40	
4.10. 0	105	3	38	Heart beats irregularly.
4.10.25		to		INJECTION OF 2 cc. COMMENCED.
4.11. 0	104		39	Heart very irregular.
4.12. 0	103	4	38	Still irregular.
4.13. 0	100			
4.13.10	96			
4.13.16	100		36	INJECTION OF 2 cc. $Na_4P_2O_7$
4.13.21	94			COMPLETED.
4.13.30	96			
4.14. 0	96		34	
4.14.30	96		39	
4.15. 0	100		34	
4.15.15	100		34½	
4.15.30	104		33	
4.15.45	104			
4.16. 0	104			
4.16.30	104		35	
4.17. 0	104		34½	
4.18. 0	100		34½	
4.19. 0	102		34	
4.19.21	102			INJECTION OF SECOND 2 cc. OF
4.19.30	104		33½	SAME COMMENCED.
4.19.40	103		33	
4.20. 0	100		32	

Experiment IV. *continued.*

Time.	Blood-pressure in mm. mercury.	No. of Respirations in 10 secs.	No. of Heart-beats in 10 secs.	Remarks.
H. M. S.				
4.20.10	87			Struggles.
4.20.20	86			INJECTION COMPLETED. For next 25 secs. the heart was most irregular; for some 5 s. no elevation perceptible, after that 4 elevations in 10 secs.
4.20.30	70			
4.20.40	67		35½	Steady B. P. curve up and then down.
4.20.53	89			
4.21. 0	64			
4.21.10	48			Steady fall. Line nearly devoid of traces of heart's action.
4.21.20	40			
4.21.25	76			
4.21.33	117		42	Abrupt rise. Heart-beats become again perceptible.
4.21.40	104			
4.21.50	95		41	
4.22. 0	99		36	
4.22.30	104		38	The respiration-curves here indicate 2-3 in 10 secs.
4.23. 0	114	2—3	38½	
4.23.30	110			
4.24. 0	110	4	38	Respirations not counted. Coincidence with respiration-curves only noted occasionally.
4.25. 0	114	5	39	
4.25.30	105	5½	42	
4.26. 0	110	6	44	Pressure very steady.
4.27. 0	110			Respiration regular.
4.28. 0	107	6	40	
4.29. 0	106	5	38	Not so regular. INJECTION OF 1 cc. COMMENCED.
4.29.30	108	5	36	
4.30. 2	106	6	35	INJECTION OF 1 cc. COMPLETED.
4.30.38	98			
4.31. 0	100	6½	35	
4.32. 0	102		32	Heart-beats irregular.
4.33. 0	102			Still irregular.
4.33.50	98		37	" " INJECTION OF 2 cc. COMMENCED.
4.34. 8	96			
4.34.30	98	7½	35	Heart-beats much more regular.
4.35. 0	97	7	36	
4.35.26	82	6	34	Heart very feeble. INJECTION OF 2 cc. COMPLETED.
4.35.45	68			Feeble action, if any, of heart.
4.36. 0	51			
4.36.25	33			Dyspnœa.
4.36.38	70		33 (?)	Heart-beats again perceptible.
4.37. 0	31			
4.37.10	40	4 (?)	38 (?)	Convulsions.
4.37.40	23		over 40 (?)	Steady fall. Heart-beats very faint.
4.38. 0	13			Apparently dead.

Pressure fell rather slowly to zero.

Exp. V. Rabbit, 2088 grms. Dose, 2 cc. of solution of pyro-phosphate of sodium, containing 2 per cent. P_2O_5 injected into ext. jugular vein.

Time.	Pulse in 10 sec.	B. P.	Remarks.
H. M. S.			
			Cord exposed ready for section.
			Kymograph at femoral artery.
4.28	20	84	Normals after all preparations have been made.
4.30	21	94	Injected $\frac{3}{10}$ cc. of 1 per cent. solution urari.
4.30.20			Injection complete (of urari).
4.31.40			Respiration almost ceased.
			Artificial respiration was commenced, 60 times per min., and kept up continuously, the bellows being regulated by means of a watch.
4.38.30	20	95	
4.48	17	120	Cord had been somewhat irritated by bleeding incident to division of the atlanto-occipital membrane. Division of cord. B. P. fell, at first quickly, then more slowly.
4.49	20	63	
4.51.30	23	38	
4.51.40			Injection of 2 cc. of solution of pyro-phosphate of soda commenced.
4.52	23	39	Immediately after this moment the heart begins to slacken, the beats becoming longer (*i.e.* slower), and the B. P. falls steadily.
4.52.20	7	25	Injection complete. Pulse became slower and slower until death.
4.53		14	Heart has ceased.
			Dead.

Exp. VI. Rana temporaria prepared for Coates' experiment. Reddish rabbit's serum used.

H. M.

2 . 40. Normal tracing taken. Heart beats vigorously.

2 . 50. A second normal, exactly similar to the first, taken. Pure serum now replaced by serum mixed with $\frac{1}{24}$th of its volume of standard solution of $Na_4P_2O_7$, containing 2 per cent. P_2O_5.

2 . 51. Auricles beating only 3-4 in 10 seconds. Ventricle contracting feebly at irregular intervals. Cannot get a tracing.

3 . 30. Ventricle tightly contracted; does not respond to mechanical irritation. Auricles continue to beat slowly.

4 . 15. Auricles still contracting slowly and slightly. Ventricles in the same state as before.

Exp. VII.

4 . 0. Rana temporaria prepared for Coates' experiment.

4 . 25. Heart beats well and fully.

4 . 35. Normal tracing taken.

H. M.

4 . 38. Pure serum replaced by mixture of 1 vol. of standard solution of $Na_4P_2O_7$, containing 2 per cent. P_2O_5, and 24 of serum.

4 . 38 . 2s. Ventricle has ceased to contract, or rather has become spasmodically contracted. Auricles beat 4 times in 10 secs.

4 . 50. On touching the ventricle, no contraction is caused; auricles continue beating very slowly.

Exp. VIII.

2 . 30. Rana temporaria prepared for Coates' experiment.

2 . 50. Normal tracing taken. Heart beating vigorously 6 to 7 times in 10 seconds.

3 . 20. Pure serum replaced by mixture of 1 part of sodium pyrophosphate solution, containing 2 per cent. P_2O_5, to 24 of serum.

3 . 21. Cessation of contraction of ventricle in diastole; auricles still beating 15 times in 30 seconds. Cannot get a tracing. Direct mechanical excitation of ventricle does not produce a contraction.

3 . 22. The part of the ventricle which was mechanically excited has now contracted.

3 . 25. Auricles beating sluggishly and feebly 13 times in 30 seconds. Ventricle responds after a long interval to mechanical excitation.

4 . 20. Auricles still contracting feebly 8 times in 30 seconds. Ventricle is distended, and does not respond to irritation.

Exp. IX. Canadian bull-frog, prepared for Coates' experiment. Reddish rabbit's serum used. Right vagus exposed.

H. M. S.

11 . 35 . 0. Ready. Heart, by vigorous beats, pumps the serum rapidly through the circulatory apparatus. Normal tracing taken.

11 . 45 . 0. Second normal tracing taken. Vagus excited. Heart stops in diastole. (Excitation produced by Du Bois-Reymond's apparatus, 1 D., secondary coil at 20 c. m.)

11 . 47 . 0. Serum replaced by a mixture of 24 parts of serum and 1 part standard solution $Na_4P_2O_7$, as above.

11 . 47 . 30. Ventricle not pulsating—firmly contracted. Auricles scarcely contracting.

11 . 47 . 45. Irritation of right vagus; complete stoppage of auricles; no relaxation of ventricle.

On excitation being discontinued the auricles do not recommence, but remain distended. Ventricle firmly contracted; pinching does not produce any results.

The serum was changed, being replaced by normal healthy serum. The heart was emptied of the poisoned serum which it contained, and filled, as far as it was possible, with fresh. Neither auricles

nor ventricle pulsate. Direct stimulation with the current and mechanical irritation each fail to cause contraction.

Exp. X. Canadian bull-frog. Reddish rabbit's serum used. Prepared for Coates' experiment. Right vagus exposed.

H.	M.	S.	
1	0	0.	Normal tracing taken. Heart contracts very vigorously and perfectly.
1	6	15.	Serum replaced by poisoned serum containing 1 part of standard solution $Na_4P_2O_7$ in 75 parts serum.
1	6	40.	Ventricle stops in systole; auricles continue beating.
1	7	0.	Vagus excited with electrical arrangements as in preceding experiment (IX.); auricles stop; ventricles do not at all relax.
1	8	0.	Auricles beat very feebly (8 in 30 seconds). Excitation of the vagus was repeated eight times with the same result, ventricle remaining firmly contracted while the auricles ceased to pulsate. The excitations occurred at intervals of about three minutes.
1	15	0.	Pulsations of auricles very feeble (5 in 30 sec.). On stroking ventricle with a steel blunt hook slight muscular contractions occurred.
1	25	0.	Ventricle somewhat more relaxed; no contraction of it on electrical stimulation. Auricles pulsating feebly; they stop on stimulation.
1	35	0.	Auricles and ventricles both at a stand-still; the latter in the same contracted state as when the next preceding note was made. No contractions follow electrical or mechanical stimulation.

Résumé.

From the experiments which have been quoted, we may arrive at the following general conclusions of the action of pyro-phosphate of sodium on the circulation, when it has been injected into veins.

The symptoms of poisonous action follow within from 6 to 25 seconds of the commencement of injection,—a difference of time, there is no reason to doubt, which is due to the greater or less rapidity of injection, and the less or greater quantity of blood in the blood-vessels of the animal experimented on. During this interval we would merely note that the appearance of the graphic records is a perfectly normal one; and that the interval, even at its briefest

is long enough to allow the drug to complete the round of the circulation.

Of the symptoms, that which generally precedes is the fall of blood-pressure. This commences as a gradual and steady descent which may last for 5 or 7 seconds without any marked variation in the pulse supervening. Always after that interval, however, and occasionally without any interval, the pulse undergoes a great change. Its rapidity suddenly sinks to less than half its former rate, and it records itself on the revolving cylinder as deep, large curves. The blood-pressure, meanwhile, continues to fall, the gradient of its descent apparently not being altered by the change in pulse. This phase lasts a variable number of seconds, *i. e.* from 10 to 35 seconds, when convulsions or violent muscular movements intervene, and raise the mean blood-pressure suddenly and in an irregular manner. The struggles last for a longer or shorter time; but, as repose is again established, the line of mean pressure is seen to resume its descent, the pulse exhibiting its former abnormal characters, or having become less rapid and feebler. This phase, if the dose be lethal, endures until death; or it may be interrupted by another paroxysm of struggles and afterwards re-appear, to remain until death. If the dose be not lethal, but still have been large enough to induce marked symptoms, the pulse at this stage does not become feebler. The blood-pressure stays its descent, or even reverses its course, and, with many irregular fluctuations due to violent strugglings, tends to its former level. The pulse also resumes its usual characters; and the tracing on the recording cylinder ultimately becomes quite normal.

If the dose be still smaller, the phases are more rapidly passed through. The descent of blood-pressure is of very brief duration, and gives place to a rise, which occasionally leads for a time to a blood-pressure considerably above the usual level. In the course of this rise the heart-beats again become normal.

There is, therefore, to be observed in cases of poisoning by pyro-phosphate of sodium a two-fold change in the circulation, (1) a fall in blood-pressure; and (2) a variation of pulse. The cause or causes of these it will now be necessary to discuss.

In the first place, these symptoms, though they must modify each other, are originally distinct. It might indeed appear that the slow and feeble heart, by driving into the arteries less blood than the latter expel owing to the tension of their walls, was the immediate cause of the diminished blood-pressure; and, unquestionably, any change in such important conditions of the normal blood-pressure as the vigour and rapidity of heart-beat, when once established, must very materially affect that pressure. But that the altered pulse originates the fall in blood-pressure is clearly not the case, since most frequently the latter precedes the former by a few seconds; and, although the two phenomena occasionally *coincided,* no case occurred in which the alteration in heart-beats was observed to come first.

In the second place, we must recall what has already been more fully discussed in another paper, viz. the action of pyro-phosphate of sodium on the muscular tissue of the heart. This action it is important to bear in mind, when it is remembered that the substance of the heart and the chief element in the vascular walls—chief, that is to say, in regard to their tonus—are composed of muscular tissue, change induced in which might possibly be called in to account for the circulatory symptoms. It would appear that pyro-phosphate of sodium is by no means devoid of action on the cardiac muscle, which, when bathed by serous solutions of it invariably fails sooner or later to respond to stimulation. But we doubt if all the effects of those solutions on the beating heart are to be accounted for solely by their action on the muscular tissue. The very curious difference in the action on ventricle and auricle—the former being at once contracted tightly, while the latter is merely slowed—is a point not to be omitted from consideration, as possibly implicating some other agent; while it must not be forgotten that the nervous centres in the spinal cord concerned in the production of movements are undoubtedly acted upon in poisoning by pyro-phosphate of sodium. It seems, therefore, not unreasonable to suppose that the symptoms described are, in part at least, due to lesion of some portion of the nervous system related to the heart and vessels.

With respect to the heart, as is well known, the ordinary

movements are caused by certain intrinsic nerve-centres which distribute rhythmically to the muscles the nervous energy necessary to produce movement. These nerve-centres are further regarded as under the control of other nerves which originate in the cerebro-spinal axis, and which can influence the distribution of that energy so as to quicken or slow, or even stop the cardiac movements. With acceleration we have here nothing to do. Hence the action of pyro-phosphate of sodium on the heart must be effected either through the vagus—the inhibitory nerve—or through the intrinsic motor ganglia. That the vagus centre is in no way affected by the poison it would be rash to assert in the face of observed facts, such as convulsions, paralysis, etc., which compel us to assume the implication of such a large part of the cerebro-spinal centres. But that it is not the chief factor, or even an important factor, is abundantly proved from the experiments of two of us recorded in a previous paper, and from Exps. V. and IV. of this series. The last-mentioned experiment (Exp. IV.) in which the drug was injected after division of the vagi in the neck, shews that the slowing and cessation of the pulse are not due—or not entirely due—to stimulation of the vagus centre: while Exp. V. where the cord was divided in a curarized rabbit prior to injection; taken in conjunction with the other experiments referred to, in which pyro-phosphate of sodium induced its usual symptoms in an atropized frog's heart, exonerate the vagus-endings and the intrinsic inhibitory arrangements connected therewith.

Hence we may believe that, whatever be the changes induced by pyro-phosphate of sodium in virtue of its being a muscular poison, the operation of the salt upon the intrinsic motor ganglia of the heart concurs in producing the cardiac symptoms.

Equally impossible is it, assuming the implication of the vaso-motor centre, to state at present how far the abolition or depression of vascular tonus is determined by peripheral stimulation of the numerous depressor nerves connected with that centre.

We must not omit to point out and emphasize a few interesting facts observed when frogs' hearts, prepared for

Coates' experiment, are treated with poisoned serum,—facts which are of special importance as bringing pyro-phosphate of sodium, as a physiological agent, into relation with pyro-vanadate of soda.

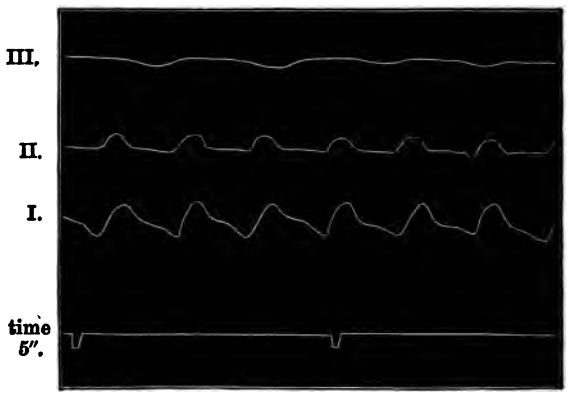
In the first place, the ventricle is instantly firmly contracted, while the auricles are simply slowed.

In the second place, the stoppage of the ventricles in systole occasionally, but very rarely, gives place to a stoppage in diastole, the auricles behaving alike in both cases.

In the third place, stimulation of the vagus-trunk, though powerful enough to stop the slowly-beating auricles, produces no effect whatever on the contracted ventricle.

In the fourth place, thorough atropization of the frog's heart does not at all interfere to prevent the usual action of sodium pyro-phosphate.

The following tracings shew the changes in the character of the heart-beats of a frog's heart prepared by Coates' method, when poisoned by dilute solutions of sodium pyrophosphate.



I. Normal tracing: prior to poisoning.
II. Shortly after poisoning.
III. Some time after poisoning.

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OBSERVATIONS ON THE PHYSIOLOGICAL ACTION OF CHROMIUM.

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I. INTRODUCTION.

WHEN engaged some time ago in investigating the physiological action of vanadium, it appeared of some interest to compare the discovered operation in the body of that metal with the operation of an element to which vanadium was at one time supposed to be closely allied, viz., chromium; for although Roscoe had established the true relationships of vanadium as a pentad metal, yet the proximity, amounting almost to identity, of the atomic weights of vanadium and chromium (V. 51·2, Cr. 52·2) rendered such a comparison of some moment in this era of bold toxicological speculation. On a search being made, however, it appeared that the exact effects of exhibiting chromium in the animal system were still unknown. The rough toxicology had certainly been learnt in the manner in which, unfortunately, much of our toxicological knowledge has come to us, viz., from cases of accidental poisoning of workmen and others. Knowledge so obtained is seldom in a comparable form; hence it became necessary, in the case of chromium, to supplement it by a systematic investigation.

This was undertaken, and the results, which I have had by me for upwards of two years, are now for the first time made public.

The exact state of our knowledge of chromium poisoning in 1874, is thus summed up by Hermann (*Experimentelle Toxicologie*): "Die Chromsalze und Chromalaune haben nach den spärlichen "darüber vorliegenden Erfahrungen ähnliche Wirkungen wie die "Aluminiumsalze.—Die Chrom-Säure ebenso, aber schwächer, das "Kaliumbichromat, auch das neutrale Kalichromat, wirkt heftiger "erbrechen- und durchfall-erregend als andere neutrale Alkalisalze. "Experimentelle Untersuchungen über diese Körper sind fast noch "gar nicht angestellt." Since then I am not aware that any contributions have been added to our knowledge of the physiological action of these bodies except a series of observations published in the last

number[1] of the *Archiv für experimentelle Pathologie und Pharmacologie* and entitled "Beobachtungen über die toxische Wirkung der Chromsäure," by Dr E. Gergens, Assistent am Physiologischen Institut zu Strassburg. It contains the details of some half-dozen experiments chiefly performed upon dogs which had had their spinal cords divided at the level of the 12th dorsal vertebra. The remarkable roughness of most of the experiments, in which the poison was introduced by puncturing the cord itself with a Pravaz syringe inserted through an aperture previously made from behind, render it impossible to attach importance to Dr Gergens' conclusions; while the paucity of the experiments alone, without considering their contradictory results, attest the crudity of the theory of action he seeks to set up. One very important result of his investigation, however, must not be lost sight of. The perfect concurrence of all his experiments proves that albuminuria, with cloudiness of renal epithelium, urinary casts and congestion of the kidneys, are concomitants of poisoning by chromic acid and neutral potassium chromate; while his control-experiments sufficiently indicate that they are referable to the drug, and not to the injuries due to the method of injection. I have brought these facts into relation with the results of my own observation, inserting them, with due acknowledgment, in their proper place in the text.

It now only remains to be mentioned that the salt used in this research was the neutral chromate of sodium ($Na_2 Cr O_4$) —to avoid any decided acid or alkaline reaction, and to secure an inert base, being specially kept in view.

It has not been deemed necessary to print a large number of protocols: those which are given may be regarded as typical cases.

II. Notes of Experiments.

Exp. I. Rabbit, wt. 1301 grm., dose 4 cc. of a solution of neutral sodium chromate containing 5 p.c. $Cr O_3$, injected underneath the skin of the back. Within 15 min. of the time of injection symptoms of poisoning set in. The head was thrown back in jerks; the hind limbs seemed paraplegic. The animal became weak and lay over on its side or back. Within 48 min. of injection the corneæ became insensitive, though pinches applied to the skin of the limbs were then felt and responded to; and in 1 min. more—49 min. after injection—the animal died with asphyxial symptoms, with head thrown back and legs outstretched.

Exp. II. Guinea-pig, wt. 422 grms., dose 1 cc. of solution of neutral chromate of soda containing 10 p.c. $Cr O_3$, injected under the skin. Within 16 min. of the time of injection symptoms of poisoning appeared. The animal became very quiet, and would not stir when

[1] July, 1876.

pushed. When, some minutes afterwards, it moved spontaneously into a dark corner, it was with difficulty, owing to a tendency to fall over on the left side. Its breathing at the same time became spasmodic. On lying down on its right side it was seized first with spasms of head and limbs, and then with severe retching. The strong spasms subsided into slighter twitches affecting the muscles of the posterior limbs and back; and, as the animal moved, its hind legs were imperfectly controlled. The retching seemed to involve the whole of the muscles, but especially those of the hind legs. 35 min. after poisoning paralysis of the posterior half of the body was well advanced, to run or to stand being impossible. Respiration came at longer and longer intervals and in painful gasps. After a final severe trial to vomit, which left the abdominal muscles strongly contracted, the animal rapidly sank; and within 40 min. of the time of injection it died.

Sectio cadaveris disclosed the following:

1. Presence of much greenish-yellow coloration in the cellular tissue punctured by the injecting syringe.

2. Congestion of alimentary tract.

The *stomach* contained a light grey thin grumous mass. It exhibited much congestion, at the back and cardiac end, of a cherry colour. Ecchymoses appeared externally and internally on the walls. Arborescent injection of chocolate-coloured blood was noticed at the pyloric end externally (the peritoneum being *in situ*).

The *duodenum* exhibited cherry-coloured congestion of mucous membrane, chiefly, but not solely, at its free border. Externally, like the stomach, it appeared much injected with chocolate-coloured blood.

The *rest of the small intestine* exhibited the same characters of congestion, but to a slighter degree. It was filled with the same gruel-like contents as the stomach.

The *large intestine* was slightly congested.

3. Partial brown congestion of lungs, viz. at the top of the right lung, and a few surface patches elsewhere.

4. The liver was deeply cherry-coloured and equally coloured throughout its mass.

5. The kidneys were somewhat congested with cherry-coloured blood.

6. The auricles were contracting. The blood, which was of a deep chocolate colour, coagulated normally. The blood of another guinea-pig, similarly poisoned, exhibited absorption-bands resembling those of methæmoglobin when examined by means of a Browning's microspectroscope.

Exp. III. Small frog. Dose, 1·5 cc. of solution of neutral sodium chromate, containing 10 per cent. $Cr\,O_3$ injected under the skin of the back.

Within 10 minutes of injection tremors of the thigh-muscles were noted. Respiration had already ceased, and the cornea was insensitive. The fore limbs were very firmly folded. Reflex action was slight, and the efforts of the frog, when laid on its back, to regain the upright position were slight, short, and ineffectual.

Fifteen minutes after injection the strongest acetic acid applied to the skin of the foot only induced slight movements; but on my trying to open his firmly-shut mouth the frog extended his hind legs once violently. This peculiar movement, not calculated at all to avoid or repel the irritant, was several times repeated, viz. once when I pinched the skin of the folded arms, again on each of two occasions when I tapped on the top of the head, and a fourth time when I turned the frog on to his back. Shortly after, about 25 minutes from the time of injection, some power of reflex movement seemed to have returned, as was evidenced on pinching the toes. All this time the before-mentioned quivering of the thigh muscles continued.

When 55 minutes had elapsed since poisoning, as reflex action was entirely abolished, the frog was opened. The heart had stopped in diastole and was filled with dark chocolate-coloured blood. The muscles were of a yellowish-brown colour. Free exudation into the cavities of the body had occurred. On testing with interrupted induced currents, the muscles, nerves and cord (as far as it is a conductor of impressions) were found to be sensibly normal.

Exp. IV. Small frog. Dose, ·25 cc. of solution of neutral sodium chromate, containing 10 per cent. CrO_3, injected under skin of back.

The right femoral artery was tied to prevent the passage of the poison to the tissues of the right leg.

Within 15 minutes of injection the arms became vigorously and continuously contracted. Respiration was slight and the cornea well-nigh insensitive. On laying the frog on his back both legs were tetanically stretched for a few seconds. The legs, which remained spread out after their tetanic extension had passed over, were not, as usual, retracted to the body when the toes were pinched, but both, on the contrary, were again forcibly stretched out.

Within 35 minutes of administering the poison the power of reflex action was entirely lost; the cornea was insensitive; but the arms still remained firmly contracted across the chest. On opening the frog the heart was found to be stopped in diastole; but it responded to stimulation, viz. on pinching with forceps.

The muscles were yellowish-brown in colour. There had been extensive exudation into the various cavities of the body. On testing with electrical stimuli, viz. interrupted induction-shocks, the poisoned and the non-poisoned muscles and nerves shewed themselves equally normal. The cord also was sensibly uninjured as far as its conducting properties were concerned.

Exp. V. July 21, 1874. Rabbit, weight 1760 grms., dose 6 cc. of a solution of neutral sodium chromate, containing 5 per cent. CrO_3, in two equal parts, injected into right external jugular vein.

Time.	Pulse in 10 sec.	B. P.	Remarks.
H.M.S.			Kymographic cannula in left carotid.
3.31	46	182	Respiration curves 11½ in 10 sec.
3.33			Struggles.
3.34·30		178	
3.35			Two or three violent struggles.
3.37			Resp. curves very marked. Pulse very marked.
3.41.30	39	184	Resp. curves occasionally shewn.
3.41.35	41	182	Injection of 1st quantity commenced.
3.41.45	38½	190	Resp. curves slight.
3.42.15	41	192	Pulse quite normal.
3.43	43	196	Resp. curves have ceased.
3.43.10			B. P. begins to fall. Pulse 41 during preceding 10 sec. and 43 during succeeding 10 sec., during which it is feebler.
3.43.20		161	B. P. ceases to fall. Injection complete. Struggles then occur which raise the B. P. to 188. Pulse vigorous. Resp. curves exceedingly well marked for 15 sec.
3.43.40	37	188	Resp. curves become imperceptible: pulse becomes feebler. B. P. falls to 160.
3.44	46		Struggles then occur, whereafter resp. curves again
3.44.5		160	become visible, and the pulse regains its vigour.
3.44.30	37	144	B. P. now slowly falls.
3.46	43	112	Resp. curves still well marked: pulse very vigorous.
3.48			Respirations 7 in 10 sec.
			Resp. curves 8 in 10 sec.
3.49.30	45	98	Respirations 12 in 10 sec.
			Resp. curves 11—12 in 10 sec., tolerably well marked.
3.54.15			Violent struggles which send up the B. P. to 164.
3.55	45	164	Resp. curves 12 in 10 sec.
3.55.30	45		Struggles; B. P. irregular.
3.56 to 3.57	43	180	Quivering convulsions of extremities. B. P. very irregular. Eye sensitive.
			Resp. curves well shewn.
3.58	41	172	Blood noticed to be very dark. Resp. curves well shewn (10—11 in 10 sec.). Pulse well marked. B. P. irregular.
3.58.30			Respirations 10—11 in 10 sec. and deep.
3.58.40			
4.	40	135	B. P. has fallen; struggles ceased. Resp. curves well marked.
4.3.10	41	78	B. P. gradually fallen. Respirations 7 in 10 sec. Resp. curves 7 in 10 sec. Pulse vigorous.
4.4.20	42	99	B. P. steadily rises. Pulse and resp. curves as before.
4.4.50		72	B. P. falls steadily. Pulse and resp. curves as before.
4.5.40	40	82	B. P. rises steadily. Pulse and resp. curves as before.
4.7	40	79	Pulse and resp. curves just as before.

Experiment V. *continued.*

Time.	Pulse in 10 sec.	B. P.	Remarks.
4.13	22—23	70	Characters of pulse entirely change: now we have long, full beats, large excursions of the pen, a second beat often following before the diastole of the preceding has run its usual course. (See Fig. 2.)
4.13.40		78	No respiration curves.
4.14			Blood looks almost black.
4.15	19	80	More of the double beats here noticed.
4.17	19	82	As before.
4.17.40			The dicrotism here occasionally seems to resolve itself into two perfect pulsations. B. P. rises.
4.18			The above is now more frequently the case. B. P. rising.
4.18.25	32	104	
4.25	27	84	Pulse regular and vigorous; no resp. curves: now and then diastole seems to elongate, giving a characteristic appearance as of "slipping" a beat. (Fig. 3.)
4.34.30	31	87	Pulse seems quite normal.
4.41.30	31	93	Resp. curves well shewn.
4.52.50	32	98	
5.17	31	127	B. P. has steadily risen.
5.17.10	31	127	INJECTION of second quantity COMMENCED.
5.18	30	138	
5.18.10			Struggle making B. P. irregular.
5.18.25		156	Injection continues. Irregularities of B. P. due to struggles.
5.18.35	30	148	B. P. Pulse and resp. curves quite regular and vigorous.
5.18.50	27	164	Pulse has become large, and exhibits the tendency to "slip" above noticed.
5.19.20 to 5.19.50	26 to 22	146 to 137	B. P. irregular. Injection complete. Cries of rabbit. Pulse large and irregular. No resp. curves.
5.20.40	23—24	157	B. P. regular; pulse large and regular. Resp. curves regular.
5.21.20	23	114	B. P. falls suddenly.
5.24	24	58	Steady fall of B. P. Pulse full and large; left eye insensitive; right somewhat insensitive. Resp. curves long and not always to be seen.
		50	Quivering of fore part of body. B. P. quite steady.
5.25.10	23	48	Struggles of whole body without any alteration of B. P. whatever: pulse seems to cease entirely.
5.26	23	46	Stretching out of hind limbs. Pulse feebler.
5.27			No respiratory movements. Pulse very feeble, long, and hardly to be counted.
5.27.30	19	38	
5.30			Dead.

Exp. VI. Rabbit, weight 2160 grms., dose 2 cc. of a solution of neutral sodium chromate, containing 10 per cent. Cr O_3, injected into vein (external jugular).

Time.	Pulse in 10 sec.	B. P.	Remarks.
H. M. S.			Kymograph at carotid.
1.16	43	208	Normals. Resp. curves 8 in 10 sec.
1.17		208	Right vagus divided.
1.17.10	45	202	
1.17.15		216	Left vagus divided.
1.17.40	46	220	
1.19	48	224	No respiration curves.
1.20.30	47	224	Injection commenced. }
1.21.11	46	226	} No resp. curves.
1.21.31			Injection complete. }
1.22	49	250	
1.25	51—53	147	B. P. has gradually fallen. Struggles followed immediately after completion of injection; but none occurred afterwards to disturb the gradual fall of B. P.
1.29.30	44	184	Pulse quite normal. Since 1 h. 25 m. there have been occasional struggles which send up the B. P. temporarily and suddenly.
	36	176	
1.37.20	38	72	Resp. curves 7 in 10 sec.
1.39	36	52	Pulse firm. Regular fall of B. P., not disturbed by struggle. Resp. curves 4 in 10 sec. Respirations were 5 in 10 sec., by direct counting, a little time previously.
1.40.30	34	44	Pulse feebler. Resp. curves slight, 4 in 10 sec.
1.42			A series of struggles begin which disturb the B. P.
1.43.30			Struggles continue, rapidly following one another.
1.45			Convulsive movements of thorax at every respiration.
1.48	34	36	Respiration ceasing. Resp. curves not to be seen.
about 1.51			The B. P. sank gradually; the pulse weakened and lengthened until the rabbit died about three minutes after.

The following figures illustrate the action of neutral sodium chromate on the blood-pressure and pulse. (The straight lines at the bottom of each figure is the line of no-pressure; the curved line is the tracing of the kymographic pen; the intermediate interrupted line, where it exists, indicates intervals of 10 seconds. The tracings are *not* reduced in size.)

Rabbit—1760 grms., dose (1) 3 cc., (2) 3 cc., solution neutral sodium chromate containing 5 per cent. CrO_3 injected into veins. See Exp. V.

Fig. 1. Normal.

Fig. 2. Tracing taken 32m. after injecting 1st dose.

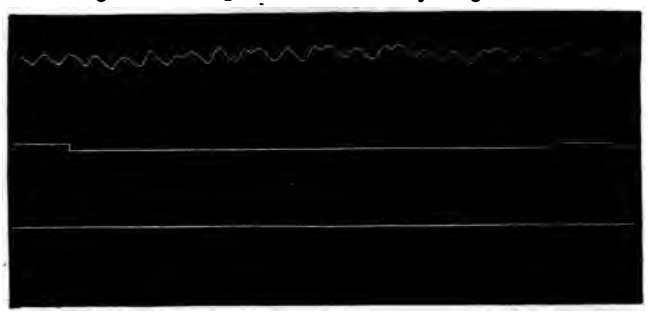
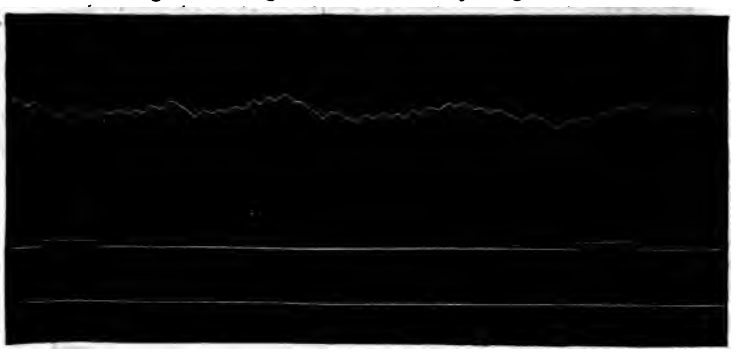


Fig 3. Tracing taken 44m. after injecting 1st dose.



Rabbit—1400. Dose 3 cc. of solution neutral sodium chromate containing 5 per cent. CrO_3, injected into veins.

Fig. 4. Normal, just prior to injection.

Fig. 5. Tracing taken 13 m. 10 secs. after injection.

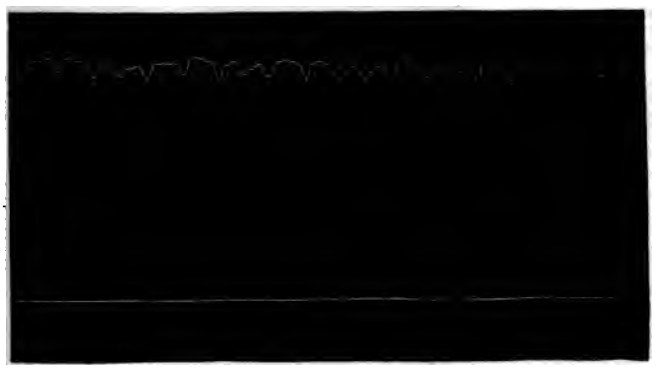


Fig. 6. Tracing taken 17m. 45secs. after injection.

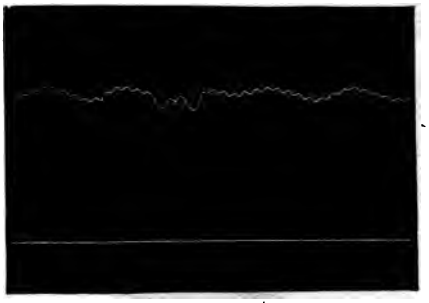
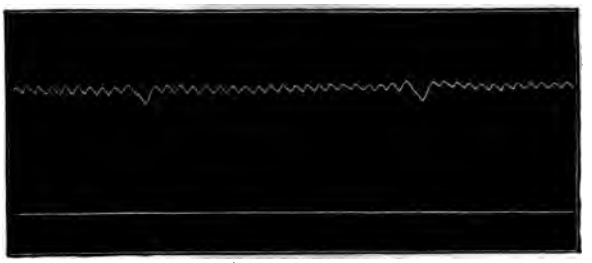


Fig. 7. Tracing about 24m. after injection. The 'slips' here were synchronous with respiration.



Rabbit. Dose 1 cc.
1 cc.
1 cc. } neutral sodium chromate solution, containing 5 per cent. CrO_3, injected into vein.

Fig. 8. Normal.

Fig. 9. Tracing taken 55m. after 1st injection, 33m. 15secs. after 2nd injection, 7m. 30secs. after 3rd injection.

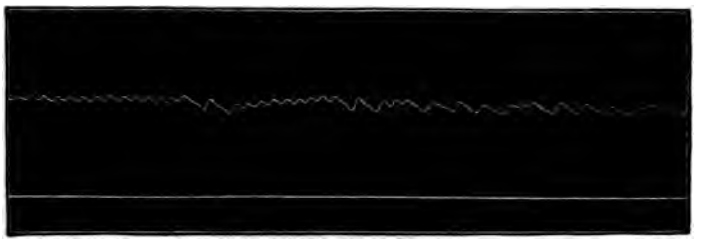


Fig. 10. Tracing taken 4m. 30secs. after the last tracing.

Rabbit[1]. 2085 grms. Dose 3 cc. (nearly) of solution of neutral chromate of sodium, containing 10 per cent. CrO_3, injected into vein. Rabbit very violent.

Fig. 11. Normal.

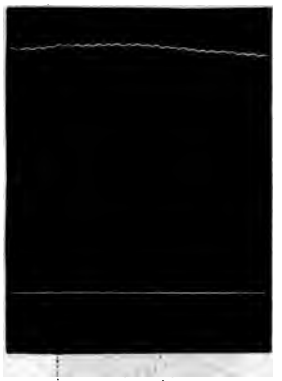
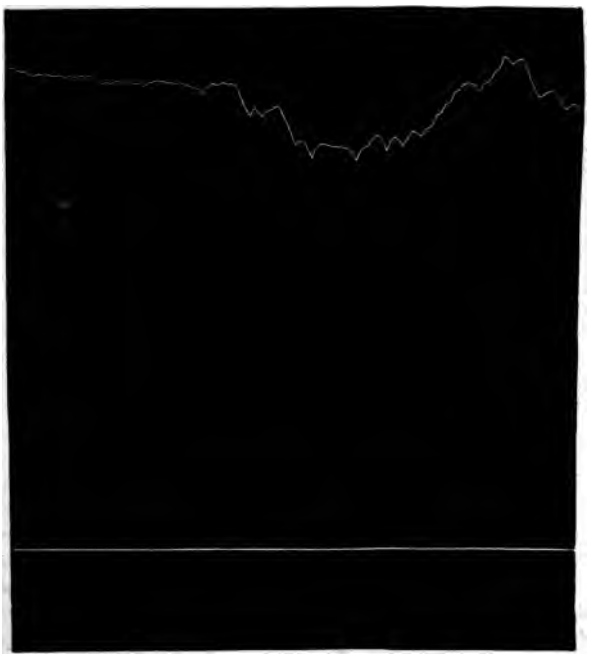


Fig. 12. During injection. Usually the rise after injection was not so marked as in this case.

[1] This rabbit had lost much blood.

Fig. 13. Tracing taken 40 secs. after injection. Violent struggles were taking place.



III. Résumé.

In brief, the symptoms of acute poisoning by chromates are as follows:

·1 to ·3 gr. CrO_3 in the form of neutral chromate of soda is a powerful poison for rabbits and guinea-pigs, producing death in from 4 min. to 30 min. (according to the vigour of the animals) if injected at once into veins; and in from 40 min. to 50 min. when introduced beneath the skin. ·15 grm. CrO_3 in the above form, when injected into a vein in three equal doses at intervals of 23 or 24 minutes, killed in 1 h. 10 m.; while ·3 grms. CrO_3 in two equal doses in the case of another rabbit took 1 h. 50 m. to cause death.

Death is preceded by spasms or convulsions, and violent retching, which commence a few minutes after the injection of the poison. In frogs muscular tremors, tetanic contraction of the pectoral muscles and the flexors of the fore-limbs, and tetanic extension of the hind-limbs on the application of slight stimuli, represent this class of symptoms. Convulsions are varied, or succeeded by paralysis of motion in mammals, and in frogs, as is usual, of respiration also. In frogs, too, the power of reflex action is speedily abolished.

The blood-pressure generally[1] rises within 10 sec. of injection of

[1] In one case only it failed to rise appreciably.

the poison into the jugular vein; but this rise speedily gives way to a fall, which begins from ¾ of a min. to 3 min. after injection. A downward tendency is steadily maintained until death, previous to which the blood-pressure becomes extremely slight; and it is only interrupted by occasional struggles with their consequent irregularities of vascular tension. Meanwhile the pulse preserves a strict normality, save that, as the blood-pressure falls it becomes somewhat deeper—a circumstance due presumably to the larger excursion of the laxer arterial walls. With this exception it appears to be quite independent of the blood-pressure, maintaining its rapidity until the latter has reached a mean equal to one-half, or one-third, of the normal. Afterward, however, a peculiar modification begins to occur at irregular intervals; and continues to appear for longer or shorter periods. After a time it gives place to a pulse of normal character, but of less than the original rapidity. Again it returns; but it invariably disappears just before death, when the pulse gradually lengthens and weakens. This phenomenon gives one the impression of the heart stopping suddenly for the space of a beat, again setting up normal pulsation immediately afterward,—as it were, 'slipping' a beat. That is to say, the blood-pressure merely continues the fall which it had initiated during the preceding diastole, and the impression gathered from the graphic record is one of prolonged dilatation of the ventricle. These slips may occur coincidently with struggles; but generally this is not the case (Figs. 1—10). On one occasion, for a space of nearly two minutes, towards the close of an experiment, they continued synchronous with inspiration. Generally they are less regular, occurring after every 8 to 3 ordinary heart-beats; and sometimes they are so lawless as to give the tracing an appearance like that of Fig. 13. They are interjected into the series of ordinary heart-beats without previous warning; and they do not seem to specially, or at once, affect the mean blood-pressure.

After these irregularities have set in, although the pulse may again become normal in appearance, it never regains its previous rapidity, but remains deep and slow.

The variations of blood-pressure, coincident with respiration, disappeared and reappeared several times after the injection of chromate of sodium into the veins; to which no importance can be attached, since they are frequently noticed to do the same in rabbits which have not been poisoned.

The *post mortem* examination of the animals experimented on disclosed the following.

The reduction of the drug in the cellular tissues at the point of injection beneath the skin, as evidenced by the yellowish green colouration.

Free exudation of fluids, in the case of frogs, into the various cavities and spaces of the body. The muscles also in frogs were of a yellow-brown colour—the colour of the original solution, and not due therefore to any reduction.

Congestion and ecchymoses of all parts of the alimentary canal

below the cardiac orifice of the stomach. Semifluid grumous intestinal contents.

Congestion of lung in the case of a guinea-pig. (It should be noted that guinea-pigs readily become afflicted with lung diseases.)

Congestion of the kidney. Dr E. Gergens has also noticed, in dogs and rabbits, cloudiness of the epithelium, urinary casts, and albuminuria, to follow poisoning by chromic acid and neutral potassium chromate.

Stoppage of the heart in diastole, even in frogs. The frog-heart, so stopped, responded but languidly to the stimulus of pinching. Chocolate colouration of the blood which exhibited the bands of methæmoglobin when examined through a spectroscope.

Muscles, and nerve-trunks and extremities, appeared to be sensibly normal.

Of these symptoms, with the exception of the variations of blood-pressure and pulse, the interpretation seems so obvious as not to need comment. Indeed even the immediate cause of the disturbance of blood-pressure can readily be seen in the face of the facts disclosed. The evident normality of pulse which continues long after the fall has become marked, at once excludes the possibility of a cardiac origin of the fall in blood-pressure. Moreover, it renders it extremely improbable that the fall was produced by a dilatation of the vessels in consequence of a direct action of the drug upon their muscular walls; for it is hardly possible that a drug should at the same moment cause rapid death of one set of involuntary muscles, viz. those of the arteries; and leave another—those of the heart—to which access is equally free, apparently uninjured. To disturbance of the vaso-motor centre, therefore, we must turn for an explanation of the varying blood-pressure. The above considerations, of course, do not exhaust the discussion of the subject; but the sustained nature of the fall of pressure makes any reference of it to a reflex origin, through excitation of depressor nerves, in the highest degree improbable; while the general aspect of the tracings obtained, and the certain knowledge that other centres in the cord, as the motor centres, are affected by the poison, place the matter beyond a reasonable doubt.

The cause of the pulse-change is not so apparent. It is, however, clear that the peculiar slips, the nature of which is far better gathered from the accompanying figures than from a description, are due to a temporary continuance of the ventricular diastole. This, I think, will be granted on a comparison with similar tracings taken from a heart stopping after stimulation of vagus.

Now prolonged diastole of ventricle may occur in consequence of one or more of three causes:

(1) Stimulation of vagus in some part of its course.

(2) Stimulation of the hypothetic inhibitory mechanism, intermediate between vagus and motor centres.

(3) Failure of muscular action due to some change in muscle-substance itself.

Of these the third may be briefly dismissed. The *formal* regularity of the pulse to the very close of life, with the exception of the

occasional slips; and the fact that the latter occur suddenly and often singly in the midst of series of regular beats; seem to eliminate from the question, as before remarked, all suspicion of muscular poisoning. The decision between the remaining possible causes is speedily made; for a reference to Exp. VI. performed on a rabbit whose vagi were previously divided, will shew that the characteristic phenomenon did not once occur. To this circumstance the fullest importance must be given; since in no case out of six experiments made on rabbits with vagi intact were the symptoms wanting. This experiment, which was confirmed by repetition, at once eliminates the second possible cause and establishes the first. Stimulation of the cardiac inhibitory portion of the vagus at some point above the level of section, *i. e.* above the middle of the neck, must, with the facts at present before us, be regarded as the efficient cause of the variations in the character of the pulse: and the preservation of the conducting powers of motor nerves during acute chromium poisoning, leaves us no alternative to considering the centre of the vagus in the medulla as the exact point of lesion.

IV. Conclusion.

As is the case with many other irritant metallic poisons, the action of chromium salts on the animal economy may be regarded as twofold, viz. an action on mucous membranes, and an action on the great nervous centres.

Of the former the evidence rests chiefly upon *post mortem* appearances. The congestion and the hæmorrhagic infarctions discovered in the internal coat of stomach, and small and large intestine, and which so rapidly follow injection of the drug; the character of the contents of the intestines, which consist of copious fluid, or but slightly viscid, grumous material, sufficiently indicate the nature of the changes which seize upon the mucous membrane of the alimentary canal: while the congestion of kidney, the cloudiness and fatty degeneration of its epithelium (Gergens), together with the occurrence of albuminuria (Gergens) with casts, shew at once the implication of the renal secreting apparatus.

As evidence of the second action of chromate-salts there are the various phenomena which have been already noticed in detail, (1) of stimulation, and (2) of depression, of various cerebro-spinal centres. Of these, as one of the most important, the vaso motor centre must be mentioned. This centre is somewhat stimulated as soon as the poison has had time to circulate to the brain, the arterial tonus being considerably

raised shortly after venous injection; but, after a brief period of exaltation, the power of the centre gradually declines; it loses its hold on the vessels, which, as death approaches, are apparently dilated to the full.

The respiratory centre in mammals would appear not to be materially injured, at least the methods of observation adopted have not been adequate to shew any abnormality; but in the frog, as may frequently be noticed in the cases of paralysis otherwise induced, the movements of respiration are the first to cease—a fact which the persisting vitality of nerve-trunks compels us to attribute to functional death of the respiratory centre.

The cardiac-inhibitory centre in the cord must also be regarded as acted upon in an irregular manner by chromate of soda, if, as I have sought to shew, the curious variations in the pulse-tracing which constantly follow poisoning by this salt are really referable to inhibition.

The motor centres of the cerebro-spinal system are manifestly acted upon. The convulsions in guinea-pigs and rabbits, followed by paralysis, chiefly but not solely of the lower extremities, and the tetanic contraction of the arms in frogs, cannot be due to any other cause. The abolition of reflex action in frogs is an analogous case, and shews that the centres concerned in the origination of motor impressions in accordance with afferent or sensory stimuli are also affected by this poison; for the abolition was due to injury neither of motor nor of sensory nerve-trunks or terminals, and must therefore have been caused by lesion of the reflecting centres.

With regard to the heart, I do not think we can attribute to chromium any direct or special action upon it. The introduction of a comparatively large amount of the strong solution of any salt into the blood must necessarily so disturb the coarser, physical characters of that fluid, as to cause it to react upon the tissues it bathes in a manner injurious to their function; but this is not, rightly speaking, a special action of the salt. In this sense only can it be said that chromate of soda affects the heart, and causes, for example, that stoppage in diastole which must be regarded as very remarkable when occurring in the frog.

It is intended, however, to enter more fully into this matter in a subsequent research.

From the *Journ. of Anat. and Phys.*, Vol. XI.]

ON THE CHANGES IN THE CIRCULATION WHICH ARE INDUCED WHEN THE BLOOD IS EXPELLED FROM THE LIMBS BY ESMARCH'S METHOD.

By H. G. Brooke, B.A. (*London*), and E. O. Hopwood, B.A. *Christ's Church, Oxford, Platt Exhibitioners in the Physiological Laboratory of Owens College.*

An idea suggested itself some time ago to Dr Gamgee that it would be interesting to observe from a physiological point of view the effects produced on the circulation by the application of Esmarch's bandages, and he therefore seized the opportunity of the presence in Manchester of Dr Paul Albrecht, late Assistant in Professor Esmarch's Clinique at Kiel, to commence a series of experiments, which we have carried on, and the results of which are here recorded.

1. Description of method of experimenting.

Our method of procedure is as follows. A strong 3 inch web elastic bandage is taken, stretched tightly under the foot of the individual to be operated upon, and over the ends of the toes, turned and wound upwards in spirals, *lege artis*, passing over a pad placed under the popliteal space in order to make more complete pressure on the subjacent vessels, and then over the thigh. At the top of the thigh two or three overlying turns are made, and the bandage is fastened by means of an ordinary safety-pin, a plan which we found to be as efficient as the use of any tourniquet, and much less painful; throughout the series of experiments we tried to avoid all actual pain in order to eliminate, as much as possible, the influence of any psychical or reflex vaso-motor effect on the pulse-rate, and we succeeded so far as to produce nothing more than a mere feeling of discomfort from the compression which the bandage necessarily exerts.

In order to see if the object has been accomplished, the bandage is removed from the foot upwards with the exception of the few folds, which serve as a tourniquet. If the bandage has been well applied the limb appears perfectly blanched, and after a period of slight hyperæsthesia (in some cases), followed

by paralysis of both motor and sensory nerves, it becomes quite cold and cadaverous. Tapping on the foot then produces the sensation of a series of shocks on the section of the thigh immediately above the 'tourniquet.' The subject was in each case stripped and in the recumbent posture, and the experiments were made an hour or two after a meal. The normal pulse-rate and sphygmographic tracings (at three different pressures) were first taken, the bandage was then applied as described, the pulse-rate being now, as indeed throughout the whole experiment, carefully and constantly counted.

On the completion of the bandaging three more tracings were taken by the sphygmograph, which was kept continuously applied to the arm. The second leg was afterwards treated in the same manner, and, after an interval, the two bandages simultaneously released, the pulse being now most carefully counted for short periods, and the observations continued until the re-establishment of the normal condition. On releasing the bandages the blood is seen to rush quickly down the leg, causing an intense blush, and, without any uncomfortable sensations, the limb in a few moments completely regains its power.

Throughout the experiments the following observations on the general conditions of the persons experimented on were made. In addition to the local alterations in sensibility, it was observed that usually some time after the bandages had been applied the individual complained of a great fulness of the eyes, accompanied sometimes by a throbbing of the iliacs and of the common carotids. After the blood had been allowed to re-enter the limbs intense shivering, sometimes almost amounting to rigor, but unaccompanied by any sensation of cold, was observed.

Five individuals, all vigorous adult males, varying between the age of 21 and 27 were experimented upon. Three of them were experimented upon on two different occasions, so that altogether eight sets of observations were made. These led to the most concordant results, which we shall proceed to state before quoting the actual data of some of the experiments.

General results of the Experiments.

1st. Whilst one lower limb is being bandaged an increase in the pulse-rate always occurs, which may continue for some

minutes, but which more commonly falls quickly to about the normal rate. 2nd. During the bandaging of the second lower limb the pulse again becomes quicker, but the quickening is only temporary; when the pulse falls after this second rise it may however remain permanently a few beats above the normal. 3rd. When both bandages are suddenly removed there is an instantaneous and usually remarkable quickening of the heart-beat, which only lasts for a very short time, and which is followed by a fall to below the normal rate, and sometimes by irregular action of the heart; this condition is usually of brief duration.

We shall now give the more important data obtained in four of our experiments.

Exp. 1. July 20, 1876. Subject of experiment, *A*. *A* is 22 years of age, weighs 140 lbs., and is 5 ft. 6 in. in height.

Time. p.m. H. M. S.	Pulse Rate in 60 Seconds.	Observations.
1 15	82	*A* has stripped and is lying on a bed, sufficiently covered not to suffer from cold. Sphygmographic tracing of right radial taking.
1 22	78	
1 24	82	Application of Esmarch bandage to left leg is commenced.
	96	During the bandaging.
1 29	88	The bandaging of the left leg completed.
1 30	84	
1 32	88	Sphygmographic tracing taken.
1 32 30	84	
1 37		Bandaging of right leg commenced.
1 40	100	The right leg is half bandaged.
1 41	84	Bandaging finished.
1 44	94	
1 47	92	
1 49	86	
1 50	82	
1 51		Bandages suddenly removed.
	108	
1 54	94	
1 55	70	
1 58	76	
1 59	74	
2 0	76	
2 4	72	

Exp. 2. July 20, 1876. *B* experimented upon. *B* is 22 years of age. Weight of *B* 168 lbs.; height of *B* 6 ft.

Time. p.m. H. M. S.	Observations.	Pulse Rate in 60 Seconds.
3 45	*B* is lying on a bed stripped.	58—62
3 52	... ...	64—66
3 53	Bandaging of right leg commenced.	56
3 58	Bandaging is proceeding.	72
3 58 30	Bandaging is completed.	72
4 1	Sphygmographic tracing taken.	58
4 6	Bandaging of left leg commenced.	58
4 9	Bandaging is proceeding.	68
4 12	Bandaging finished. Feels fulness of head. Sphygmographic tracing taken.	60
4 15	... ...	62
4 19	Both bandages simultaneously removed. In the two succeeding half-minutes the pulse was 44 in 30 seconds	88
	42 „	82
4 24	... ...	58

Appended is the set of sphygmographic tracings. It will be observed that in this case tracings (2) and (3) do not indicate any quickening of the pulse, the rate of which had fallen before the tracings were taken.

Tracings (4) illustrate well the quickening which immediately follows the return of blood to the limbs. It will be observed that the lowest of the three tracings in (4) shews a much more rapid pulse than the second and third; in the few seconds which elapsed between the taking of (1) and (3) the frequency of the pulse had diminished remarkably.

Tracings (5) illustrate how perfectly the pulse returned to its normal rate and form after the bandages had been taken off.

Tracings taken in Exp. 2. *B.* July 20, 1876.

Fig. 1. Normal, before bandaging.

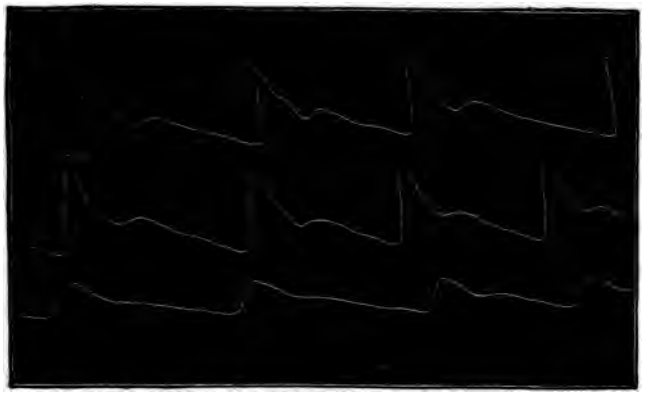


Fig. 2. After one leg has been bandaged.

Fig. 3. After both legs have been bandaged.

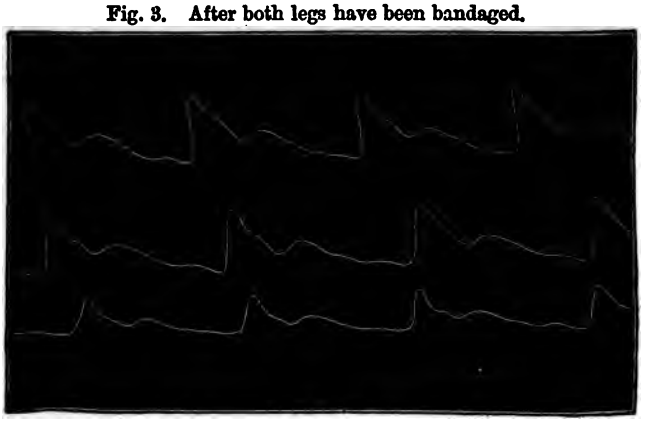


Fig. 4. Immediately after unbandaging.

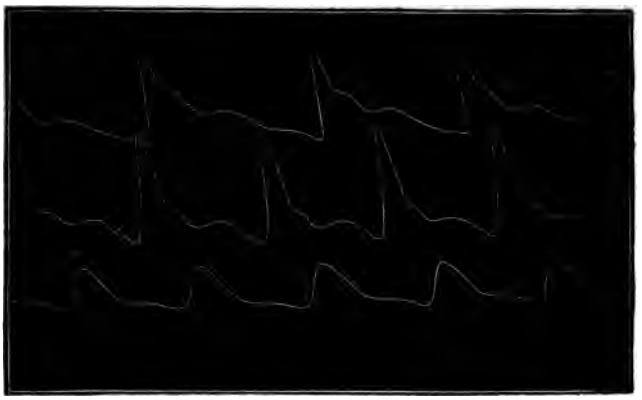
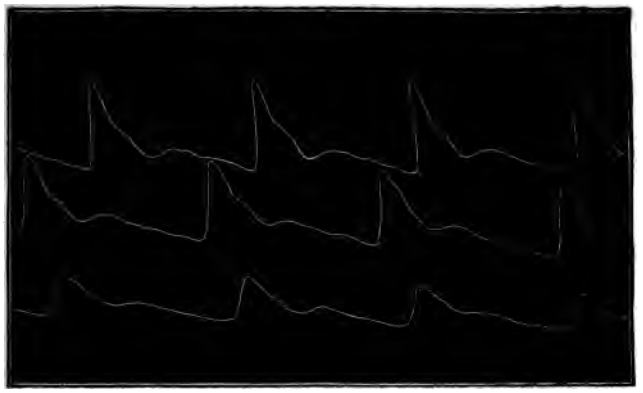


Fig. 5. Some time after unbandaging.



In all cases the lowest of the three tracings which was taken first is at a pressure of 3 oz., the middle curve at 4 oz., and the highest curve at 5 oz.

Exp. 3. May 19, 1876. Individual experimented upon, *C*. Age of *C* is 21; weight 140 lbs.; height 5 ft. 11½ in.

Time. p.m. H. M. S.	Observations.	Pulse Rate in 60 Seconds.
8 5 to 8 12	Is lying recumbent on a bed.	70—74
8 16	... ...	62
8 17 15	... ...	63
8 19	... ...	66
8 23	Bandaging of left leg commenced. Pulse during each successive 30 seconds throughout the bandaging counted 36 in 30 seconds.	
	35 ,,	
	39 ,,	
	38 ,,	
	37 ,,	
	44 ,,	
	44 ,,	
	or at the rate of	88
8 39	Bandaging is completed.	68—70
	Complains of fulness of eyes.	72
8 41	... ...	70
8 50	Anæsthesia of left foot.	
8 51	Bandaging of right leg commenced.	62
8 53	Pulse 35 in 30 seconds.	
8 53 30	35 ,,	
8 54	38 ,,	
8 54 30	38 ,, ...	76
8 55	36 ,,	
8 55 30	38 ,,	
8 59	44 ,,	
8 59 30	48 ,, ...	92
9 0	45 ,,	
9 1	45 ,, ...	90
9 3	Bandaging completed.	
9 4 30	Pulse 36 in 30 seconds.	
9 5	34 ,,	
9 5 30	34 ,,	
9 6 45	37 ,,	
9 7 15	37 ,,	
9 7 45	Suffering a little from palpitation.	70
9 8	... ...	66
	Left leg unbandaged.	
9 12 30	... ...	72
9 14 30	Right leg unbandaged.	
9 15	Shivering of whole body, but without any feeling of cold.	68
9 16	Shivering and tremor of all the muscles. ...	69
9 17	Chattering of teeth.	

Exp. 4. *C* was experimented upon exactly as before.

	H.	M.	S.	
At	2	55		Bandaging of right leg was commenced.
	2	59		Bandaging of right leg completed.
	3	5		Bandaging of left leg commenced.
	3	10		Bandaging proceeding; complains of fulness of eyes.
	3	12	30	Bandaging of both legs completed.
	3	23		Both legs unbandaged.

As the tracings in this case illustrate more visibly the quickening which immediately followed bandaging of first and second leg, they are given without a table of pulse-rates. Tracing (4) does not shew the quickening which followed unbandaging, too long a time having elapsed between this event and the taking of the tracing. The pulse was however observed to rise from 78 to 92 in the minute following unbandaging.

Tracings taken in Exp. 4. *C*. July 20, 1876.

Fig. 1. Normal, before bandaging.

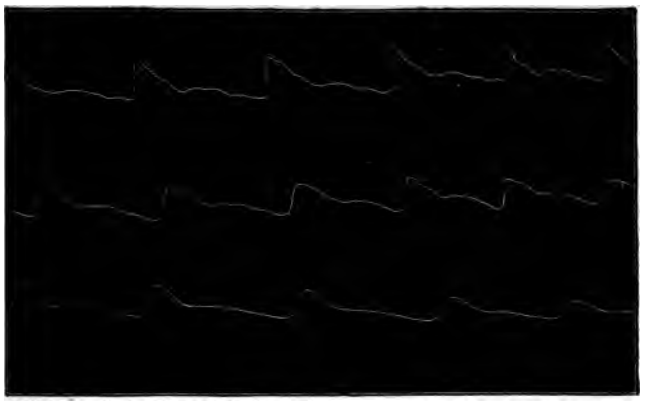


Fig. 2. After one leg had been bandaged.

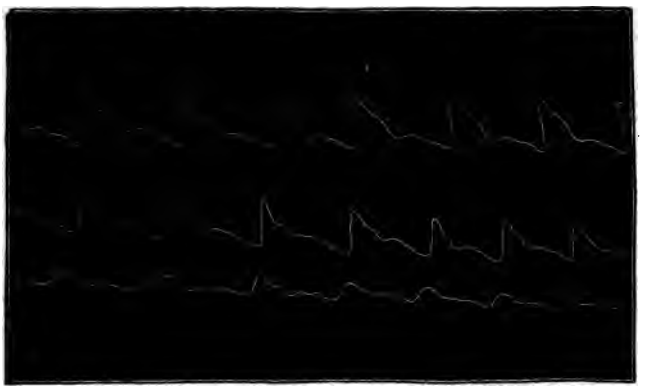


Fig. 3. After both legs had been bandaged.

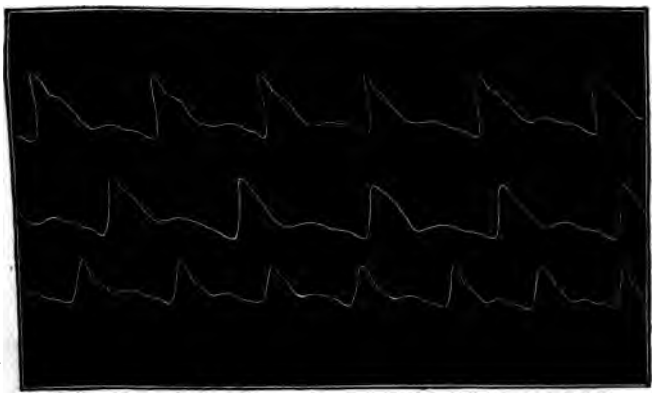
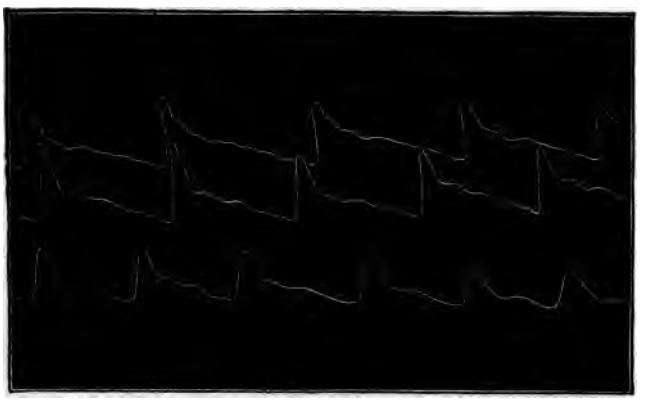


Fig. 4. After unbandaging both legs.



In all cases the lowest curve, which was taken first, is at a pressure of 3 oz., the middle curve at 4 oz., and the highest curve at 5 oz.

Analysis of the changes induced in the Experiments.

Having illustrated by a sufficient number of facts the phenomena which were observed to follow the expulsion of blood from the limbs by Esmarch's method, we think it well to examine the influence which the bandaging and unbandaging must exert upon the blood-pressure in arteries and veins.

When Esmarch's bandages are applied to one or both lower extremities the following results must follow.

Firstly. Blood is expelled from the capillaries and veins of the compressed part. The cadaveric whiteness of the part is a proof of the emptying of the capillaries. It is certain that nearly the whole, if not the whole, of the blood contained in the limbs is expelled by Esmarch's method[1].

Secondly. Blood is expelled from the arteries, part of it passing into capillaries and veins, but part also being pushed back into the arteries of the trunk.

Thirdly. Lymph is expelled from the lower extremities in considerable quantity, and increases the amount of lymph emptied into the venous system.

There can, we believe, be no doubt that the effect of these three sets of events must be to increase for a time the pressure in the venous system to a greater extent than the pressure in the arterial system. Our reasons for this belief are briefly the following:—

The amount of blood contained in the capillaries and veins of the limb, or even in the latter alone, is very much greater than that contained in the arteries, so that if the effect of the bandaging were merely to add arterial and venous blood to the arteries and veins of the trunk, we should say that more venous than arterial blood entered the trunk as the result of the bandaging. But the effect of the quantities of arterial and venous blood thrown into the body upon the pressure in the right and left sides of the heart cannot be measured merely by their relative amounts; we must take into consideration likewise the capacity of the portion of the vascular system which has the extra quantity of blood added to it. Now any increase of pressure at any point of the arterial system may affect more or less, it is true, the blood-pressure in the arteries of all parts; not so with the veins, for the blood which is thrust into say the iliac veins, when one lower limb is compressed, will have no influence on the blood-pressure in the veins of the other lower limb or of the upper extremities. The presence of valves will limit the increase of pressure due to this addition of blood mainly to the veins of the trunk; we should therefore assume

[1] Labord and Mord d'Arlaux state from their own experiments that the veins are not completely emptied by the compression; M. Krishaber asserts that in man there is found to be an entire absence of blood in the veins.

that, notwithstanding the greater capacity of the veins as compared with the arteries of the trunk, the effect of the application of Esmarch's bandages to both lower limbs will be *for a time* sensibly to increase the relative pressure on the right side of the heart.

The addition of lymph forced out of the compressed lower limbs will tend to increase still further the relative venous pressure—it will have, however, another effect which must not be neglected; the effect to which we allude is a modification of the chemical characters of the blood of the right side. It is indeed possible that a small increase in the amount of lymph entering the great veins may exert a marked influence upon the action of the heart, as this organ is now known to be exceedingly sensitive to very minute differences in the chemical composition of the blood supplying it[1].

On the other hand, when Esmarch's bandage is removed the effect is suddenly and extensively to increase the vascular area by adding to the vessels of the trunk and upper extremities the vessels of both lower limbs. But again, the change does not equally affect the arterial and venous systems. Owing to the inter-position of valves it may be asserted that the accession of area affects merely the arteries. In consequence, the arterial tension suddenly diminishes while the venous tension is not immediately touched; the *relative* pressure in the right heart as compared with the left, has increased; in other words the normal *difference* of pressure between the two sides of the heart is lessened; and, in fact, the same change, but otherwise induced, has occurred after unbandaging as after bandaging.

Theoretical explanation of the Phenomena.

It is with diffidence that we trust ourselves to speculate at all in this matter: not only on account of the presence of an unknown factor in the effect on the heart of the added lymph: but also on account of our imperfect, merely general, knowledge of the action of afferent nerves in reflex connection

[1] This influence of the lymph as affecting the *quality* of the blood and thus influencing the action of the heart was pointed out to us by Professor Kronecker when an abstract of this paper was read before the Physiological section of the British Association in September, 1876.

with the heart. Is it not possible, for example, that the changes we have observed may be due to the stimulation of afferent nerves, other than sensory, ramifying in the tissues of the leg—a stimulation determined by the expulsion and readmission of blood? But setting aside the possibility that further discovery may suggest additional causes of the phenomena, the hypothesis we are about to advance appears competent to connect the facts already observed, and may turn out to be at least a partial explanation.

It has been stated that bandaging and unbandaging the lower limbs produce the same series of effects on the pulse-rate. It has further been shewn that both operations lead to disturbances of vascular tension exactly similar in nature though differently conditioned: that is to say, in both cases, the difference which normally exists between the venous and arterial pressures is diminished, on bandaging, by approximating the venous to the arterial, and on unbandaging, by approximating the arterial to the venous pressure.

May we not seek in this coincidence of conditions the cause of the altered heart-rate? In order to do so it must be assumed that such a diminution of the normal difference of venous and arterial pressures leads to accelerated pulsation of heart. This assumption is not so important as it may at first sight appear: for it is but a more general expression of a proposition advanced long ago, and often insisted upon by Professor Marey.

M. Marey has shewn that when the arterial pressure is increased the heart beats more slowly; when the arterial pressure is diminished the heart beats more rapidly. He has cited a large number of cases, which shew that all those acts of the body which lead to vascular dilatation are necessarily accompanied by a rapid action of the heart. Thus when we run the muscular vessels dilate and the heart beats rapidly. When the body is heated the same effect follows, whilst when it is cooled the heart beats more slowly. Now we may, if we like, say that in these cases the primary cause of the rapid or slow heart-beat is the diminution or increase of the arterial pressure; we believe, however, that it is not unlikely that the proximate cause is to be found in the increase or diminution of the pressure in the right side of the heart.

In all the cases quoted by M. Marey in which the heart beats more rapidly, the normal difference in pressure is diminished: *i.e.* the pressure in the right side is relatively increased, and in all the cases in which the heart beats more slowly the pressure in the right side is relatively diminished. Thus dilated arterioles permit the blood to flow rapidly and in larger quantity into the veins, thus lowering the arterial and raising the venous tensions, and so reducing the difference normally existing between them. On the other hand, contracted arterioles have just the opposite effect.

This hypothesis, therefore, at the outset, receives much support from the facts and arguments of Professor Marey. But it does not lean solely upon them. In the first place, the experiments of Blasius on the work done by the frog-heart prove that, in the frog-heart, when the arterial pressure is constant the heart-rate, up to a certain point, increases as the venous pressure.

In the second place, in the pathological conditions which lead to an engorged right side, the heart's action is permanently quickened: for example, in mitral stenosis, whenever there is venous engorgement, the heart beats more rapidly.

Thus, if the view proposed of M. Marey's law be accepted, the experiments of Blasius and the case of mitral stenosis, not before covered by the law, are brought into relation with the well-known effects of increased or diminished arterial tonus, as well as with our own observations.

The various facts of the present research are accounted for in the following manner:

1. When the limbs are compressed, the quickening is explained by a diminution of the normal difference in the blood-pressure *due to the increase of pressure on the right side.*

2. The return to the normal or to near the normal rate after one limb has been compressed is due to the fact that the normal relative difference has been re-established.

3. The quickening when the limbs are unbandaged is due to a diminution of the normal difference in the blood-pressure, *owing to a decrease of pressure in the left side.*

It is quite conceivable that in the first case the right side of the heart may initiate the more rapid contractions of the whole organ, and that in the second case the left side may do so[1].

[1] The reader is referred to a paper which has appeared since this article was written, entitled, "Ueber die Abhängigkeit des Herzrhythmus von den Blutdruckschwankungen von Dr S. Tschiriew in St Petersburg:"—*Centralblatt für die medicinischen Wissenschaften*, 1876, No. 35, p. 609. The author has observed an acceleration of the heart to follow, when compression of the abdominal aorta has been kept up, and is then stopped.

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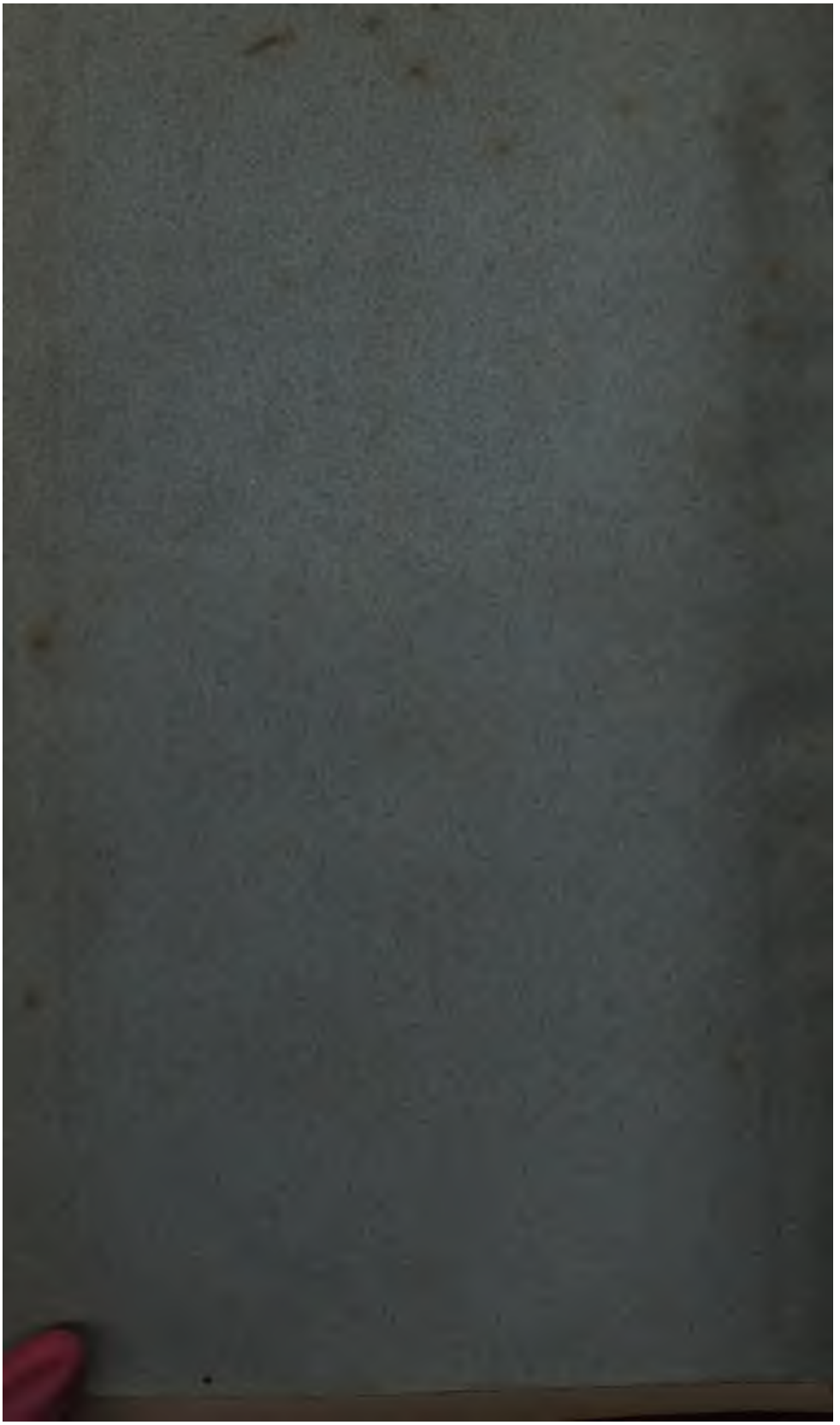
Line of no pressure

Respiration Ceased



Profess Allen F.R.S.
from the Editor

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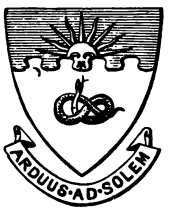

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CONTENTS.

PAGE.

Mr. PRIESTLEY, An Account of the Anatomy and Physiology of Batrachian Lymph-Hearts (mainly Bibliographical). 1

Mr. PRIESTLEY, Contributions to the Physiology of Batrachian Lymph-Hearts 19

Prof. GAMGEE and Mr. PRIESTLEY, Concerning the Effects on the Heart of Alternate Stimulation of the Vagi 39

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THE

JOURNAL OF PHYSIOLOGY.

AN ACCOUNT OF THE ANATOMY AND PHYSIOLOGY OF BATRACHIAN LYMPH-HEARTS. (Mainly Bibliographical.)

By JOHN PRIESTLEY, *Assistant Lecturer in Physiology in Owens College, Manchester.*

(*From the Physiological Laboratory of Owens College.*)

INTRODUCTION.

IN 1876 Professor Arthur Gamgee suggested to me to investigate the Lymph-hearts of Frogs. A preliminary search among the books at my disposal at the time led me to believe that the knowledge of their physiology was in a very imperfect state. Conspicuous, as it now seems, was the absence of all but the primitive discoveries from certain important text-books. Thus Ludwig (*Lehrbuch der Physiologie des Menschen*, 1861), Wundt (*Physiologie*, 1873), Quain and Sharpey (*Anatomy*, 1875) and Carpenter (*Principles of Human Physiology*, edited by Power, 1869), merely mention the existence of Lymph-hearts; Ranke (*Physiologie*, 1872) and Hermann (*Physiologie*, 1874) leave the question of their innervation entirely open, omitting at the same time the invaluable practice of appending the names of those who had investigated the subject; while Longet (*Traité de Physiologie*, 1869–70) and Kirkes (edited by Morant Baker, 1876) leave the matter as it existed about the year 1850.

Misled by this silence, and having then no means of further information, I spent some time in working out the innervation of the lymph-hearts; and when I had made experiments enough to draw up

a scheme of their nervous connections I had the partial satisfaction of finding my results confirmed, so to speak, by anticipation.

Thus I had observed the normal irregular rhythm, the function of the abdominal and dorsal branches of the tenth or coccygeal spinal nerve, the reflex inhibition by strong sensory stimulations, the constant inhibition proceeding from the encephalon, and the spring of that constant inhibition in the optic lobes; as well, of course, as the pulsation which sometimes occurs after destruction of the spinal centres.

These, and one or two facts already published*, and not, to my knowledge, taken note of by previous observers, formed the substance of a paper which was nearly in the printer's hands before I became possessed, through the great kindness of Professor Hermann, of a list of the Lymph-heart literature. So complete was the agreement between the work of previous observers and my own that I determined to suppress altogether the publication of mine.

But it has since been suggested to me that the absence from the Text-Books of allusions to a complicated nervous mechanism, curiously similar to that of the blood-heart, as it had been the cause of my work, might excuse its publication. I have, therefore, ventured to publish anew, in the form, rather, of a bibliographical paper, what doubtless is already well known to many readers. I have done so with less hesitation as I am now in a position to add something† (as I believe) to our knowledge of lymph-heart innervation.

I have not had time to repeat every observation described in the following paper. But I have given my authorities in every case; and where it seemed necessary I have pointed out my agreement or disagreement with previous observers.

I have much pleasure in thanking my friend Mr H. G. Brooke, B.A., late Platt Physiological Exhibitioner, for valuable assistance rendered during the earlier parts of the research.

Anatomy and Physiology of Batrachian Lymph-Hearts.

The lymph-hearts in *Rana temporaria*, *R. esculenta* and *R. pipiens* are four in number—an anterior pair and a posterior pair.

The anterior pair are situated, one on each side of the body, beneath the scapula and resting upon the third cervical vertebra (Müller[1], Panizza[2])‡.

* *Studies from the Physiological Laboratory in Owens College*, Part I. Preface, 1877.

† In a paper which immediately follows this.

‡ For the references see p. 17.

The posterior pair are situated one on each side in the angles formed by the convergence of the coccyx and the iliac bones (Müller[1], Panizza[2]). They are covered over by the strong *fascia ilio-coccygea* which is bound to the skin just behind the lymph-hearts by a strong laminal process. Each posterior heart, together with the loose pigmented connective tissue surrounding it, fills up an aperture that forms a passage directly into the cavity of the abdomen. This aperture is triangular in shape, with its apex pointing forward and a little outward, and hence has an internal, an external and a posterior border—an anterior, an internal and an external angle.

The internal border is formed by the lower edge of the *m. ilio-coccygeus* which runs from the coccyx forwards and outward to the iliac bone of its own side. The external border is formed by the *m. glutæus medius* as it arises from the iliac bone. The posterior border is formed by the *m. pyramidalis* running from the coccyx to the femur.

At the external angle, looked at from behind, a small portion of the *m. ilio-psoas* is to be seen through the aperture as it arises from the iliac bone. At the internal angle looked at from behind a similar portion of the *m. levator ani* presents itself to view.

Past this aperture at its external portion the ischiatic artery and nerve run in the abdomen from before backward keeping in front of the *m. pyramidalis.* Hence, looked at from before, this artery and nerve must be counted as lateral relations of the lymphatic heart.

In the triangular space just described the heart is suspended rather nearer the external than either of the other angles.

Both the anterior and posterior hearts are known to be supplied by spinal nerves (Volkmann[3]).

To the anterior hearts this supply is transmitted from the cord, through the anterior root of the second spinal nerve, and along a branch which is given off by the nerve as soon as it escapes from the intervertebral foramen and which runs backward over the anterior border of the transverse process of the third vertebra (Volkmann[3], Eckhard[4], Schiff[5]).

To the posterior hearts the supply is transmitted down the tenth spinal, or coccygeal nerve. This nerve arises by a posterior root emerging from the cord just below the posterior root of the ninth spinal nerve, and by an anterior root emerging from the cord at about the same level (Waldeyer[12]). The anterior root is sometimes double or threefold, in which cases the accessory roots come off from the cord somewhat lower down (Waldeyer[12]). The two roots run separate for some distance in

the interior of the coccyx, uniting in the spinal ganglion. From this ganglion which is lodged in a lateral foramen of the coccyx emerge the two main branches of the nerve, viz. the *ramus dorsalis* and *ramus abdominalis.*

The *r. dorsalis* at once penetrates the substance of the *m. ilio-coccygeus* and runs on its dorsal aspect downward and outward to cross the lymph-heart; it then bends upward through the ilio-coccygeal fascia to its distribution to the dorsal skin. It gives off branchlets which lose themselves in the pigmented connective tissue surrounding the lymph-heart (Waldeyer[12]).

The *R. abdominalis* also runs downward and outward, but on the abdominal aspect of the ilio-coccygeal muscle. Besides offsets to the ischiatic plexus of nerves, the sympathetic system of nerves and along the iliac artery, it supplies twigs which Waldeyer has traced through the pigmented environment into the substance of the heart itself.

The lymph-hearts are further in close relation with the sympathetic system of nerves (Waldeyer).

In the neighbourhood of the anterior hearts a small group of ganglion-cells may be seen, from which fibres run towards the hearts alongside the offsets from the main spinal nerves (Waldeyer[12]).

On the dorsal surface of the ilio-coccygeal muscle, or rather upon its *fascia propria*, two or three small groups of ganglion-cells may, according to Waldeyer, be discovered; and between the groups sympathetic fibres are seen to pass on their way to the pigmented tissue of the heart. In the interstices of this pigmented tissue Waldeyer saw, under favourable circumstances, *i.e.* when the pigment-cells were sparse, small heaps of ganglion-cells.

The posterior pair of hearts are supplied with blood from the iliac (ischiatic) artery (Waldeyer[12]).

The anterior pair of hearts pour the lymph they have collected from the axillary lymphatic spaces into a branch of the jugular vein which opens into the vena cava superior (J. Müller[1]).

The posterior pair of hearts collect lymph from the lymphatic vessels and spaces beneath the skin and between the muscles of the thigh, as well as from a superficial dorsal vessel and occasionally from a small lymphatic accompanying the aorta. They pour it into a venous branch opening into the ischiatic vein which soon afterwards becomes the *vena renalis advehens* (J. Müller[1]).

Recklinghausen[9] injected finely divided bodies—vermilion, lycopodium, etc.—suspended in appropriate vehicles, into the lymph-spaces

of the thigh, and thus was enabled to track the course of the lymph through the posterior lymph-hearts into the *vena advehens.*

As regards their minute anatomy the hearts consist of three layers: an outer, compared by Waldeyer to an adventitia, a muscular media, and an epithelial lining. The epithelium consists of tesselated cells of round or oval form. The muscular fibres constitute a close interlacing mass; the fibres themselves being small, anastomotic (Leydig[8]) and possessed of many nuclei. Amongst the muscular fibres are to be found pigmented corpuscles, together with nerve-fibres both pale and medullated, but no ganglion-cells* (Volkmann[3], Waldeyer[12]). The adventitia consists of connective tissue bearing many pigment-cells (Leydig[8], Hyrtl, Waldeyer[12]).

The lymph-hearts pulsate with a somewhat irregular rhythm. Johannes Müller called attention to the mean rapidity of beat, about 60—70 times a minute, as well as to the facts that the members of each pair of hearts do not beat synchronously with each other, or with the blood-heart, or with the respiratory movements. But he did not notice that the pulsation is by no means regular or continuous. If a frog be stretched out upon a plate of cork by means of looped cords slipped over the arms and legs and passed through slits in the edges of the plate, the posterior lymph-hearts may be seen now and then to stop suddenly without any apparent cause. After a delay, the duration of which is generally a few seconds, but occasionally longer, the hearts commence to twitch, one heart usually beginning a little while before the other. The twitchings in a few seconds give place to full beats, which, at first not periodic, soon fall into the usual rhythm.

Moreover, if the frog struggles, whether of its own will, or in consequence of irritating its skin, the posterior hearts may very frequently be noticed to stop suddenly a few seconds before the paroxysm begins, and occasionally also as long as it lasts. When the paroxysm is over-past the hearts, as a rule, beat very rapidly for a few seconds, then quickly fall to the normal rate, and within a minute after the struggle, stop. Under these circumstances stoppage may last 1—2 minutes, the hearts beginning again in the manner before described, viz. 1st as twitchings, 2nd as occasional beats, 3rd as regular pulsations.

In other cases violent exertion merely leads for a short time to accelerated pulsation, increasing the rate of beating very considerably for about a minute.

All these facts may be more easily observed after reflecting the

* A cursory examination has led me to the same conclusion.

skin over the posterior lymph-hearts by means of a T-shaped incision in the middle line of the body. If this be done it is further seen that the rhythm of the beats is not quite regular. The periods are not all of the same duration, short sharp beats disturbing the regular series; hence the two hearts, beating independently, often overtake each other and are never long coincident in their pulsations.

All the above-described variations may not occur in all frogs. For instance, it is not every frog whose lymph-hearts are brought to rest after a violent struggle. But a given frog will, in most cases, constantly exhibit the same variation. Thus a frog whose posterior hearts stop spontaneously without reference to movements will exhibit that peculiarity again and again.

These irregularities are not to be ascribed to the forced position of the frog; since the more obvious of them, as, for example, the stoppage of pulsation, may be noticed when the frog is gently held in the hand or at rest on the table.

If now the cerebro-spinal nervous centres be destroyed by pithing, the lymph-hearts come suddenly to rest, and occasionally never move again. Oftener, however, they remain at rest from $\frac{1}{4}$—$3\frac{1}{4}$ minutes (Eckhard[4], Schiff[5]). After this pause various portions of the muscular substance of the lymph-hearts begin to twitch or flicker irregularly, so that the hearts may be tugged hither and thither, or may exhibit general but confused movement (Volkmann[3], Eckhard[4], Schiff[5]). Occasionally these irregular contractions, from affecting a few muscular bundles at a time, extend to the whole at once, causing, in short, single full beats, which alternate with the flickers before mentioned. The cases where full regular beats occur are, however, infrequent (Schiff[5]). The time these altered movements last varies very much. Volkmann and Eckhard never saw them endure beyond $\frac{1}{4}$ hr. after their appearance; Schiff on the other hand saw them from 4 to 6 and even in one case to $16\frac{3}{4}$ hrs. after destruction of brain and spinal cord. There can be little doubt that the time is determined by the vigour of the frog used.

If the spinal nerves running to the lymph-hearts be severed from connection with their centres, the same effects are produced as follow destruction of the brain and spinal cord (Volkmann[3], Eckhard[4]). Thus if the nerves supplying the anterior pair be cut across at any part of their course, in root, trunk, or branch, a brief, or it may be a permanent stand-still of the hearts ensues. The same result follows section of the posterior set of nerves. To ensure success care must be

taken to divide the coccygeal nerve either as it escapes from the foramen in the side of the coccyx (Eckhard[4]), or as it is about to enter the immediate neighbourhood of the heart (Waldeyer[12]). This is necessary in order to cut off both dorsal and abdominal branch; for there can be no doubt that the fibres supplying the hearts run now in the one and now in the other. Sometimes, when the nerves have been divided in the above manner, the hearts never beat again; but most often, after a short pause, flickers or indefinite twitchings appear, which may fall occasionally into regular beats, as in the case of total destruction of the cord; and which, after an interval of many days, may give place to a normal rhythmical pulsation quite independent of the spinal cord (Goltz[11], Waldeyer[12], and confirmed by myself).

Even after excision the lymph-hearts have been seen on a few occasions to beat for a short time with vigour (Waldeyer[12], Goltz[11]); but the exact conditions of such pulsation have not yet been discovered: *e.g.* it is not known whether or not ganglion-cells were still attached to the hearts. I have once or twice seen hearts contracting vigorously when nothing was left of the frog they belonged to but the lower third of the pelvis and the stumps of the amputated thighs.

Waldeyer, I believe, is the only observer who has tested by experiment the connection of the lymph-hearts with the ganglia situated in their neighbourhood. In all Waldeyer's experiments excision of the connective tissue containing the ganglia and forming a common meeting-ground for all nerves, spinal and sympathetic, supplying the posterior hearts, led without fail to a permanent standstill of the lymph-heart of the same side.

Reviewing the statements just put forward it is clear that the lymphatic hearts may exhibit muscular movements; sometimes regular, but in the great majority of cases irregular, after their complete separation from the spinal nervous centre.

Respecting these movements of extra-spinal origin it should be observed that they are invariably at first irregular or confused twitches; if they do give place to rhythmical or almost rhythmical beats, it is only after a long interval of indefinite flickering. Their character is such as to suggest comparison with the præ-systolic twitches described above as heralding the returning beat after a normal inhibition; and these again, perhaps, with the præ-systolic movements of the blood-heart. While they have not only been compared with the confused spasms of a voluntary muscle which follow rough section of its nerves, but they have been referred to a similar cause, viz. the operative pro-

cedure (Volkmann[8], Eckhard[7]). This explanation is however not satisfactory; for the spasms of voluntary muscle under the above-mentioned circumstances soon pass off, while those of the lymph-hearts that follow section of their spinal nerves or destruction of the cord may remain for hours. Hence in order to make use of the explanation we must assume that ordinary muscle or nerve, or both, speedily become habituated and insensible to the stimulus of death-changes in the nerve, while the muscle and nerve of the lymph-hearts do not so soon establish a tolerance. This again would imply the assumption of peculiar properties either for the lymph-cardiac muscles or for the nerves. But it will afterwards be shown that the muscles do not differ from ordinary striated muscle; while the only distinction apparently possessed by the lymph-cardiac spinal nerve is a higher minimal stimulus—a peculiar property not favourable to the above hypothesis*.

The occurrence and persistence of the extra-spinal twitches seem to have relation to the vigour of the frogs used. The lymph-hearts of sluggish frogs, as a rule, quickly stop (and in many cases at once) on section of the spinal cord below the level of their centres. If the steps of the experiment have involved extensive bleeding, thus if the frog whose hearts are to be tested have been decapitated and eviscerated, the lymph-hearts exceedingly rarely, in my experience, have flickered more than a few seconds after destruction of their spinal centres. Bleeding the frog through the snipped ventricle leads after a short time to flickerings, and, in about an hour, to standstill of the lymph-hearts; and here the lymph-hearts offer a marked contrast to the blood-heart.

Whatever may be the primary cause of the movements, I have often noticed that "pumping" with the hind-legs, or moving them rapidly to and from the position of extension, would lead to a series of fairly vigorous flickers in posterior hearts separated from their spinal centres, and at other times quiet or nearly so. But that a lymph-current (such as might be supposed to be set going by the "pumping") is not necessary to the movements is shown by the fact that the movements may occur in hearts practically excised. It seems, however, that nerves are indispensable; for, in the first place, the extra-spinal twitches whenever present may invariably be annulled by dropping curare in solution upon the hearts; and in the second place, no amount of "pumping" can induce the hearts of a curarized frog to move at all.

Another theory of the movements exhibited by lymph-hearts cut off

* See the paper succeeding this.

from their spinal centres, was first clearly enunciated by Heidenhain[6] and supported mainly by Goltz[11] and Waldeyer[12, 13]. According to it, the spring of the lymph-cardiac movements is to be sought for in the neighbourhood of the hearts themselves; while to the spinal centres is assigned the function of co-ordinating the movements into rhythmical pulsations; and Waldeyer boldly asserts that the motor-centre properly so called is constituted by the ganglia to be seen near (but not amidst the fibres of) the hearts.

This theory strictly speaking resolves itself into two parts, (1) that the spinal nerves ministering to the lymph-hearts do not enter the muscular substance immediately, or at least are connected with it in a peculiar manner; and (2) that the ganglion-cells are the medium of the connection, or in some way are implicated in it. In the present state of physiological speculation, when the sharpness of our conceptions of the function of ganglion-cells is certainly dissolving, we shall do wisely to ignore the second part of the theory; for it cannot be assumed that Waldeyer's experimental excision of the nerve-ganglion and pigmented connective tissue surrounding the hearts settles the matter, when it is remembered that standstill so very frequently occurs even when that tissue is uninjured. Nevertheless there are some grounds for maintaining a view of a peculiar, mediate, connection of spinal nerve-fibres and lymph-cardiac muscles; for, not only does the actual occurrence of the beats demand some explanation, but the greater minimal stimulus of the lymph-cardiac spinal nerves seems to suggest a more complicated connection between them and their index-muscles than is to be found in the case of other striated muscles.

But whatever these movements may be in their origin, it is clear that the cerebro-spinal centres exercise control of some nature over the motions of the lymph-hearts. If the spinal cord be divided at the level of the atlanto-occipital articulation, the hearts (the posterior pair) pause in diastole for about 30 seconds. After this interval they suddenly begin again with great rapidity and regularity (Suslowa[14, 15]). They continue rapidly beating for several minutes, after which the rate of pulsation declines, but with diminishing velocity. All the time the beats are determined in character, never hesitating or interrupted as they are before section of the medulla. With vigorous frogs which have lost little blood the hearts maintain a rapidity much above the usual rate for two or three days; and even under less favourable conditions when the heart-rate sinks to the normal or below it, pulsation remains regular and unbroken.

If the spinal cord be divided at any point between the atlanto-occipital articulation and the body of the 5th vertebra the same results ensue, viz. (referring to the posterior hearts) a brief pause followed by considerable but declining acceleration of beat*.

If however the level of section be carried beyond the body of the 5th vertebra, *e.g.* if the cord be divided between the 5th and 6th vertebral arches, the consequences are altogether different, resembling in short the consequences of destroying the cord or of dividing the fibres of the coccygeal nerves.

Volkmann was the first to notice that the regular pulsation of the lymph-hearts depended upon the soundness of limited areas of the spinal cord. He found that destruction of the contents of the spinal canal opposite the 3rd and opposite the 8th vertebræ causes the anterior and the posterior pairs of hearts respectively to stop beating, destruction at the anterior spot not affecting in any way remarkable the beating of the posterior hearts; and *vice versâ*. Sections of the cord at points intermediate between the 3rd and 8th vertebræ brought about no change in the movements of either pair. He noticed, however, that frequently the hearts would come to rest even when the above-mentioned regions of the cord were, to all appearance, unhurt; and that, occasionally, the mere division of the cord in the dorsal region had the same result. In my own experiments with the posterior hearts I have met with the like discrepancies.

If the cord were to be divided while still within the spinal canal, section in the interval between the 5th and 6th vertebral arches would usually produce the desired change. Sometimes division between the 4th and 5th arches was enough.

If the cord and column were to be snipped through with scissors, section between the bodies of the 4th and 5th vertebræ was most often effective: but section between the next preceding pair had in many cases the same results. On one occasion however the spine was cut through between the 4th and 5th, between the 5th and 6th and between the 6th and 7th in succession before the usual change was brought about.

Some of these discrepancies may perhaps be readily explained. In

* Suslowa further observed that in accordance with Brown-Séquard's Law, lateral hemisection of the cord produced complemental effects on the two sides, viz. exalted activity on the side of section and depressed activity or even standstill on the opposite side. Hence the inhibitory fibres are to be found, in the cord, on the same side as the centre they are running to.

the first place, as the frog is usually held for such sections in the operator's left hand, facing away from his right hand, the point of the knife is apt to be thrown rather forward in the spinal canal instead of being just at right angles to the cord: hence division with the knife is actually rather more anterior than division with the scissors, although each is made between the same pair of vertebræ. In the second place the rougher method, with the scissors, will in all probability cause death of the divided cord to a greater depth below the exposed surface; hence the vulnerable part may be reached by one mode but not by the other, although the plane of section is the same in each*.

It is hardly possible to agree with Volkmann in saying that the part of the cord opposite the 8th vertebra is that which must be kept uninjured to ensure the rhythmical beating of the posterior hearts. Firstly the cord at that point is represented by the delicate *filum terminale*, the true cord apparently ending at the level of the 7th vertebra in *R. esculenta* and *R. temporaria*. Secondly, the coccygeal nerves which are known to minister to the posterior hearts emerge from the cord alongside the *filum terminale* also at the level of the 7th vertebra.

From the foregoing experimental facts it has been concluded (1) that there are centres in the spinal cord of the frog, one near the 3rd and one near the 6th (not the 8th) vertebra, which give origin to the rhythmical pulsation of the anterior and posterior lymph-hearts respectively; (2) that there is a higher centre situated above the atlanto-occipital articulation and capable of inhibiting the lower; and (3) that the inhibitory centre is constantly in action.

These conclusions are borne out by many other experiments. Thus, if the spinal nerves running to the lymph-hearts, or the cord whence they proceed, be stimulated by means of electric currents, contractions of the lymph-hearts ensue (Eckhard[7], Schiff[5]). The plan I adopted to demonstrate this is the following:—If a frog be decapitated and rapidly eviscerated, the skin, fore limbs and abdominal walls removed, so as to leave nothing but the spine, pelvis and legs with their attached muscles; and if all the nerves still remaining be divided, except the coccygeal; the posterior lymph-hearts may be seen beating with vigour and rapidity. In such a preparation section of the whole spine between the 5th and 6th vertebræ causes instant stoppage of the posterior hearts, after which it is extremely rare to observe in them any further movements. If a constant current (from 3—6 small Daniell cells) be passed

* Possibly also the centre may vary somewhat in position in the cord; and the cord in the spinal canal.

across the end of the cord thus exposed at the 6th vertebra once a second by means of a *Stromunterbrecher*, rhythmical contractions of the lymph-hearts and of the few muscles supplied by the coccygeal nerve may be observed, the rhythm corresponding with the rate of the interruptor. At first the contraction of hearts and muscles is so rapid and simultaneous that it is hard to discriminate the pulsations of the former; but after the current has passed in the manner described for several minutes, the muscles, unaccustomed to repeated stimulation, give feebler and more transient responses. In consequence, diastole of the hearts occurs a fraction of a second after the muscles are relaxed, and the pulsation ceases to be obscure.

Before dividing the spine between the 5th and 6th vertebræ the upper end of the cord may be stimulated by means of induced currents of moderate strength. On inserting the tips of the electrodes into the end of the cord prior to passing the current the lymph-hearts are usually brought to rest in diastole, beginning again to beat in a few seconds. On passing a current which is strong enough to affect slightly the dorsal and coccygeal muscles the hearts may be slowed or stopped. Stimulation should not be prolonged or oft repeated, for the inhibitory fibres seem readily to tire. It is, probably, for this reason that entire inhibition cannot be maintained, by continuing stimulation, beyond a few seconds.

In addition to electrical stimuli Suslowa employed chemical stimuli, with the same results; and he recommends the anterior hearts as preferable for showing the diastolic nature of the standstill that follows stimulation of the higher parts of the cerebro-spinal axis.

The higher, inhibitory, centre hitherto spoken of as existing somewhere above the atlas vertebra, was described by Goltz and after him by Waldeyer, as situated in the medulla oblongata; but Suslowa has shown that it exists much higher. Stimulation by NaCl of the optic thalami, the optic lobes, and—though less perfectly—of the medulla oblongata all cause diastolic standstill of the two pairs of lymph-hearts; and hence the centre inhibiting the lymph-cardiac pulsations must be placed alongside that controlling reflex action.

The function of the different centres governing the lymph-hearts is further illustrated by the action of anæsthetics. If a frog be placed under a small bell-jar, together with a cloth containing chloroform or pure ether, it will, by violently leaping, endeavour to escape. As insensibility creeps on, the lymph-hearts, previously normal in the character of their pulsation, may be seen beating with great rapidity and regu-

larity, like the heart of a frog with divided medulla, rising from a rate of 60—80 per min. to one of 100—120 or more. After a short time the hearts beat less vigorously. The loss of vigour speedily increases until, rather suddenly, the hearts stop. About the same time, or a little before, the legs have become perfectly limp and all signs of life have departed. If at this point the frog be drawn from underneath the bell-jar and exposed to the air the hearts soon regain their power of contracting, beating now as rapidly as before they stopped. If chloroform has been used, and its use continued until the lymph-hearts have stopped, the frog rarely recovers, or only after many hours, the rigor of chloroform most often ensuing. If on the other hand pure ether has been used recovery is sure and speedy. One by one the lost powers come back: pinching the skin causes, first, slight movements and then purpose-like acts; respiration, always lost early, is again set up, at first as faint infrequent gasps. All this time the lymph-hearts are abnormally rapid and continuous in their beating; but as the frog sits up and consciousness returns they become slower, less regular, and finally quite normal. On replacing the frog under the bell-jar the symptoms recur in the same order; but they succeed one another more quickly, owing to the previous saturation of the frog by ether vapour. In the case of chloroform the first effect on the higher nerve-centres is one of stimulation. Whether this is generally the action of chloroform on the lymphatic inhibitory centres it is impossible to determine; for the violent movements of the frog during the earlier stages of narcosis have themselves an accelerating action on the lymph-hearts which would effectually mask any slowing due to stimulation of the inhibitory centre.

With regard to the final cessation of lymph-cardiac movements caused by anæsthetics it should be noted that those lymph-hearts which are beating after separation from the spinal centres are also brought to rest under the same agents.

It has long been known that the lymph-hearts of frogs are in connection with nerves of the afferent system. Schiff[5] pointed out that strong sensory impressions led to transitory stoppage of the hearts; and Goltz[11] discovered that in the *Klopfversuch* the blood-heart and lymph-hearts behave alike. Goltz[11] further noticed that repeatedly squeezing the auricles of the blood-heart also causes prolonged diastole of the lymph-hearts; in which observation, as well as in the last, he has received confirmation from Waldeyer[12].

The mechanism of this reflex inhibition is interesting. The stimulus

of striking the abdominal viscera would seem to pass first of all to the highest centre, or, at least, to traverse the medulla oblongata either before or after reflection, since division of the medulla beneath the atlanto-occipital membrane prevents the inhibition (Goltz[11]). The same may be said of squeezing the auricles, which is of no effect after division of the vagi, whose roots are traceable into the same region of the cord (Goltz[11]).

On the other hand I have observed that pinching or lacerating the skin often inhibits the posterior hearts of frogs hours after the medulla has been divided at the usual level and the brain in front destroyed.

But whatever be the nature of the afferent nervous stimuli of the lymph-hearts, such stimuli seem unnecessary for the rhythmical pulsations of the hearts. Volkmann showed that in a headless frog, division of the posterior root of its proper spinal-nerve, after section of all the other nerves of the body, caused no stoppage of the lymph-heart; and the spinal cord of a decapitated frog may, as I have observed, be split in the plane of the fissures, without prejudicing in the least, or as far as I have noticed, modifying, the motions of the hearts. This is obviously best to be done opposite the anterior hearts where the greater thickness of each half of the cord protects the centres from accidental injury by the knife. Thus in correspondence with the independent rhythm of the hearts of opposite sides, the centres are seen to be totally separate from one another, and to derive their impulses entirely from their own side of the body*.

* Suslowa (*loc. cit.*) makes a curious statement affecting the reflex connections of the lymph-heart, which I have not yet tried to confirm. He says:—(5) Wenn man dem Frosche alle in das Rückenmark eintretenden Wurzeln durchschneidet und das Thier sich erholen lässt, die hinteren Lymphherzen in einen dauernden Stillstand (natürlich diastolischen) verfallen, und (6) Dass diese Ruhe in eine dauernde Thätigkeit übergeht sobald man dem Thier alle *Rami Communicantes* zwischen dem Rückenmark und der sympathischen Kette durchschneidet (*Centralblatt*). Further:—Wenn man einem Frosche mit den in Folge der Durchschneidung aller sensiblen Rückenmarkswurzeln stillstehenden Lymphherzen den Kopf abschneidet, oder den Schnitt an der oberen Grenze des verlängerten Marks führt, die Lymphherzen unmittelbar darauf in eine bis zum Tode andauern Thätigkeit versetzt werden (*Zeitsch. f. rat. Med.*).

According to this view the movements of the lymph-hearts are constantly controlled by opposing afferent stimuli, exciting and inhibiting. Of these the exciting stimuli traverse the sensory spinal roots, while the inhibiting run in the sympathetic communicating branches and the spinal cord, to reach the encephalic inhibitory centre. In support, Suslowa quotes and confirms Waldeyer's[13] observation that the lymph-hearts may be induced to contract by pinching the skin. On the other hand Schiff (*loc. cit.*) has stated that sensory stimuli which cause general tetanus in a strychnized frog lead to no tetanus of the lymph-hearts, but merely to an ordinary contraction.

With regard to the influence of the blood-circulation upon the pulsation of the lymph-hearts, Schiff[5] has stated that if all the vessels springing from the base of the heart are deligated, the lymph-hearts soon come to rest. If the apex of the ventricle be cut off in a brainless frog, and the blood let flow, the lymph-hearts become slower and slower in their beating and at length flicker and stop. This occurs within an hour from the time when bleeding began. Shortly afterwards it may be noticed that the power of reflex action, manifestly decreasing before, has departed from the spinal cord. That this is due to the functional death of the spinal motor centre and not to the stoppage of the lymph-current into the hearts, is shown by the following experiment. If the aorta, vena cava inferior, and abdominal vein of a brainless frog be ligatured on a level with the top of the kidneys, whereby the lower half of the trunk and the hinder extremities are deprived of blood, while the spinal cord is still supplied by means of its vertebral artery; and if, as an additional precaution, all the tissues of the hind legs, except the sciatic nerve, be severed from the trunk; the posterior pair of lymph-hearts may be seen beating with sensibly undiminished vigour for more than two days.

Moreover, section of one, or of both, sciatic nerves near the hip-joint does not alter the beats of the posterior lymph-hearts, although such a section involves great dilatation of blood-vessels in a large region supplying them with lymph. And tightly ligaturing one or both thighs close to the trunk is equally ineffectual; although by such a procedure a large portion of the lymph usually flowing into the posterior lymph-hearts is intercepted.

The influence of respiration upon the lymph-hearts, though not peculiar, is deserving of notice. Pulmonary respiration may be abolished altogether without affecting their movements, as Schiff[5] proved by cutting the vagi and thus closing the glottis; but if, besides pulmonary action, cutaneous action be stopped, by ligaturing the pulmo-cutaneous vessels, and immersing the frog in an oil-bath (Suslowa[14]), the lymph-hearts become feebler and feebler, and finally cease to move. Before the latter event happens, however, the higher inhibitory centre seems to enlarge its hold upon the lower motor centres of the hearts; for division of the medulla at the atlanto-occipital membrane is, at this stage, followed by a more marked acceleration of the posterior hearts than when such division is practised in the normal, arterialized frog (Suslowa[14]).

Conclusion.

The salient points of the normal Anatomy and Physiology of Lymph-hearts may now be indicated.

1. The hearts are muscular sacs, the fibres of which branch and freely anastomose, and are transversely striated. Their walls are penetrated by medullated and non-medullated nerve-fibres, and small nerve-ganglia are situated in the neighbourhood of the hearts; but no ganglion-cells have as yet been recognised amidst the muscular fibres. They collect the lymph from more or less extensive lymphatic regions and force it past valves into large veins, the anterior pair of hearts into branches of the jugular, the posterior pair into branches of the ischiatic vein. They are supplied by nerves from the spinal cord, the anterior pair by the second, the posterior pair by the tenth spinal nerve.

2. The hearts exhibit throughout life a pulsation with a mean rate of 60–70 a minute. It is, however, not continuously regular, being interrupted by pauses, and by periods of great acceleration. The pauses sometimes follow movements on the part of the animal, but often they cannot be set down to any definite cause. After such pauses, the pulsations begin as twitches before falling into beats of normal fulness. The periods of acceleration also seem to be determined for the most part by movements of the animal.

3. The hearts are governed by cerebro-spinal centres,—motor and inhibitory. The motor-centres are situated in the spinal cord, those for the anterior pair opposite the 3rd, and those for the posterior pair opposite the 6th vertebra. They transmit their impulses down the appropriate spinal nerves of their own side of the body; and each is independent of the rest. They originate the normal rhythm of the hearts, and their action, whatever its exact nature, is automatic, or not due directly to afferent stimuli: hence no change in the lymph-current traversing the hearts can alter their rhythm. The inhibitory centre is situated in the encephalon, in the optic lobes; it is constantly in action.

4. These centres are in connection with afferent nerves. Strong stimuli, applied to the blood-heart or to the abdominal viscera, lead to inhibition of the lymph-hearts, if the upper centre is intact. While

strong sensory stimuli, applied to the skin, may inhibit the lymph-hearts whether the upper centre is present or not.

5. But, though governed by the above centres, the lymph-hearts seem capable of an irregular pulsation when separated from them. Such pulsation consists of flickers and indefinite confused twitchings, for the most part, which, when the heart is vigorous, harmonize occasionally to full beats. The nature of these movements is still doubtful. The most that can be said about them is, that they are probably not solely muscular, since curare abolishes them.

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CONTRIBUTIONS TO THE PHYSIOLOGY OF BATRACHIAN LYMPH-HEARTS.

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INTRODUCTION.

SINCE the discovery of lymph-hearts in the Frog, by Johannes Müller and Panizza in 1832–3, much attention has been bestowed upon their nervous anatomy and physiology. This attention has been largely owing to the interest which has in the same time centred about the innervation of the blood-heart. Nevertheless, neither the blood-heart nor the lymph-hearts can as yet be said to be thoroughly understood.

While engaged in working over the normal anatomy and physiology of lymph-hearts, it occurred to me that to institute a very careful comparison between the lymph- and blood-hearts, might lead to a mutual illumination of their nervous arrangements. On the one hand, we have in the lymph-heart a rhythmically contracting muscle, that can be separated from its nerves, by curare, as readily as can an ordinary voluntary muscle. Hence we may examine, quite apart from the nervous system, the properties of a muscle that pulsates throughout life. On the other hand, if such a comparison led to close analogies in function between parts of the mechanisms of the two hearts, we might see in such analogies a clue to the innervation of the lymph-hearts.

A comparison of this nature would comprise an investigation of the effects of the cardiac drugs upon the lymph-hearts, and an examination of the action upon them of electrical currents.

Unfortunately, I am not able just now to conclude the work, but I hope to do so at a future day. In the meantime, I publish the observations I have already made.

I. ON THE ACTION OF ELECTRICAL CURRENTS ON THE LYMPH-HEARTS.

i. On the Action of Induced Currents.

The muscles of the voluntary system are more differentiated than the muscles of the blood-heart, or the muscles of the intestines, arteries,

and ureter. But this differentiation only affects certain non-essential parts: and the difference between either kind of involuntary muscle on the one hand, and voluntary muscle on the other, becomes even less if Engelmann's*, and Foster and Dew-Smith's† view be correct, that the muscular substance of the ureter, or of the blood-heart, forms a physiological whole. For then the whole heart or the whole ureter (Engelmann), must be likened to a single muscular fibre of the voluntary sort, since each is a contractile mass, throughout which nuclei are scattered. In this light, the sarcolemma becomes even a less important distinction, than it is if the so-called cells of involuntary muscle are regarded as the structural units. On the other hand, the curious tendency to become fibrillated or to cleave in planes at right angles to one another, which all muscular tissues of the body may exhibit, seems a strong indication of essential identity of structure.

Be that as it may, there are, physiologically speaking, but two sorts of muscular fibres, viz., those which, under ordinary rapidly succeeding stimuli, contract rhythmically and know no tetanus; and those which, under similar stimuli, contract continuously or exhibit a tetanus. This capacity or incapacity to maintain a constant contraction, would seem to argue very important differences in the internal economy of the contractile matter—differences no doubt affecting what we may call the commissariat. It appeared, therefore, a matter of interest to determine (what has not yet been determined beyond all question, even in the case of the tip of the ventricle, viz.), whether muscle entirely deprived of all nervous connections has ever the power of relaxing in the face of a strong stimulus, and getting ready for another contraction; whether, in fact, muscles exist which at a given moment possess available energy for one contraction only.

In order to test this, I made the following experiments. A frog recently decapitated was taken, and the skin of the back divided so as to expose the posterior lymph-hearts. The thighs were amputated close to the pelvis to prevent disturbance during stimulation: and all the spinal nerves were divided close to their vertebral foramina, except the tenth or coccygeal which supplies the posterior hearts. The division of the spinal nerves is best effected by laying the frog on its belly, and,

* Th. W. Engelmann *Zur Physiologie des Ureter. Pflüger's Arch.* II. p. 243, XI. p. 465; Th. W. Engelmann, *Centralblatt*, 1870, No. 18, p. 281.

† Foster and Dew-Smith, "On the Behaviour of the Hearts of Mollusks, &c." *Proceedings of the Royal Society*, No. 160, 1875. Also *Studies from the Physiological Laboratory in the University of Cambridge*, Part ii. p. 98; Part iii. p. 2.

with a stroke of the scissors, cutting through the posterior body-wall from top to bottom on each side, parallel with the tips of the vertebral transverse processes. In this way, the vertebral column and attached pelvis, forming a strip of the posterior body-wall, still connected with the rest of the animal by the lower end of the pelvis, may be lifted up, and the blood-vessels, sympathetic nerves, kidneys, etc., separated from its under surface. By the same act, the nerves of the ischiatic plexus are exposed to view, and may be divided one by one. The vertebral column may then be let fall into its former position, and maintained in it by means of pins passed through to the table.

After doing this, the spine was snipped through with scissors opposite the 7th vertebra, or between the 6th and 7th; whereupon, the hearts usually came to a dead and permanent standstill. If they at first exhibited twitches or movements of any sort, I waited a short time until these had ceased.

A pair of ordinary non-polarizable electrodes were then placed in position, one at each side of the anal extremity of the pelvis, at the ends of a line passing through the lymph-hearts, and just where the stump of the thigh joins the side of the pelvis. The non-polarizable electrodes formed the two ends of the secondary coil of a Du Bois' induction apparatus, in the course of which was a key breaking the wire to both poles at the same moment. The primary coil was worked by a single Grove's cell, and also had a key in its course. The current equalizer of Helmholtz was not used. Sometimes I observed the effects of the current on both hearts: but usually one heart was more favourably placed towards the light than the other, and in consequence received greater attention; observations were begun with the secondary coil far enough removed from the primary to be of no effect, and the coils were gradually approximated.

Under these conditions, lymph-hearts were examined of frogs that had been curarized either by local application of a strong solution, or by injection into the dorsal lymph-sac of a drop of solution capable of inducing paralysis in about 15 minutes. In the latter case, it was unnecessary to divide the spinal nerves, or to cut off the lymph-hearts from their spinal centres. However curare had been administered the results were the same; and what the results have been, will perhaps be best seen from the following notes of experiment.

Exp. I. 8 h. Injected 2—3 drops of strong solution of curare into dorsal lymph-sac.

8 h. 20 m. Perfect paralysis of frog.

9 h. Frog already prepared as above described, omitting section of spinal nerves and division of spinal cord. Electrodes placed in position; hearts quite still.

Time.	Distance between coils in cm.	Remarks.
h. m.		
9	8	Tetanus of interpolar muscles: hearts not affected.
	7	Tetanus of interpolar muscles, especially of ilio-coccygeals, but not of hearts (?).
9 2	6	Hearts begin to be affected by the currents.
9 2 to 9 15	6 to 0	I made very numerous trials with various strengths of current: the result being in most cases a perfect, firm tetanus of the hearts lasting the whole time of passage of current. Occasionally the hearts would twitch a few times during stimulation, but always, I think, when other interpolar muscles were twitching through exhaustion or some other cause.

Exp. II. 8 h. Injected 2—3 drops of strong solution of curare into dorsal lymph-sac.

8 h. 20 m. Perfect paralysis of frog.

10 h. Prepared frog as in last experiment.

Time.	Distance between coils in cm.	Remarks.
h. m.		
10 4	7	Passed currents for 1 m. 15 s. Firm tetanus of all parts between electrodes, including the lymph-hearts: towards close of stimulation the ilio-coccygeals exhibited a few twitches, jerking the coccyx to one side.
10 10	9	Same result as at 10 h. 4 m., except that the twitches of certain of the interpolar muscles appeared sooner. I believe there were now a few similar quivers of the left heart, but certainly none whatever of the right, which remained in firm tetanus.
10 30		From the time of the last trial until 10 h. 30 m. several trials were made with the same general result; but now no tremors or twitches whatever occurred to mar the experiment.

Exp. III. Frog decapitated. All nerves, except the tenth, divided. Thighs amputated. Electrodes placed in position, as described above, while the hearts were yet beating. Divided spine between 6th and 7th vertebræ. Hearts quite still.

10 h. 49 m. Dropped strong solution of curare on the lymph-hearts.

Time.	Distance between coils in cm.	Remarks.
h. m.		
10 52	6	Tetanus of interpolar muscles. *Perfect systole of lymph-heart almost the whole time of passing stimulus* (*i.e. nearly* 60 *sec.*). Towards the close of stimulation the heart relaxed gradually; then came a slight twitch or two, and at the same time a few fibres of the ilio-coccygeal muscle were observed to twitch.
10 55		Again bathed with curare.
11	5·5	Tetanus of interpolar muscles, quite free from twitches. Perfect systole of lymph-heart, slowly and evenly giving way to relaxation towards the close of stimulation, which lasted 60 sec. *No movements of any kind followed relaxation.*
11 2	5	Tetanus of interpolar muscles, quite free from twitchings. Lymph-heart behaved exactly as at 11 h. during stimulation, which lasted 2 min., *i.e.* perfect systole, giving place to relaxation unmarred by any movements whatever.

From these and similar experiments, we may at once conclude that the muscles of the lymph-hearts entirely detached from their nerves by means of curare can be thrown into tetanus that differs in no sensible respect from the tetanus of ordinary striated muscle.

After this result, the suggestion is obvious to try the effect of interrupted currents on the lymph-cardiac spinal nerves. This may be done at two points in their course, either as the nerve is crossing the ilio-coccygeal muscle to reach its destination, or just as the nerve has left its centre in the spinal canal, where it may be stimulated, together with the *filum terminale* of the cord, and the members of the ischiatic plexus.

In either case but little modification in the experimental steps is needed. In order to practise stimulation in the ilio-coccygeal region, the shoulder-girdle and the whole of the abdominal viscera which have been separated from the under surface of the spinal column as already

described, must be removed, by cutting through the skin, etc., that still binds them to the lower part of the pelvis. Further, the thighs must be amputated, as well as the nerves of the ischiatic plexus divided. The remnant of the frog, consisting of spinal column and pelvis, may then be suspended vertically by means of a clamp, and a pair of fine platinum electrodes slipped beneath the abdominal branch of the tenth nerve as it runs from the coccyx downward and outward. When this has been done, the hearts may both be seen beating vigorously and regularly. All that is now needed to complete the preparation is, to divide the abdominal branch of the tenth nerve above the electrodes, taking care so to divide it, as that it shall be kept stretched over the electrodes by means of the connective tissue binding it to the face of the ilio-coccygeal muscle. If the heart of the same side stops, we know that its spinal nerve descends in the abdominal branch of the tenth nerve; if it does not stop, it is perhaps more convenient to prepare another frog than to hunt for the dorsal branch—the alternative path of the lymph-cardiac fibres—and place the electrodes beneath it.

In order to practise stimulation of the lymph-cardiac nerves while yet in the spinal canal, the following plan was adopted. Before dividing the spine to separate the posterior hearts from their spinal centres, the back of the 8th vertebral arch was removed. The spine was then divided between the 6th and 7th vertebræ; and when the hearts were quite at rest, one non-polarizable electrode was inserted into the window at the back of the 8th vertebra, and the other applied to the exposed end of the cord.

As the consequence of many experiments, I am inclined to believe that, wherever their nerves are stimulated, the lymph-hearts behave like an ordinary muscle-nerve preparation, except that they have a much higher minimal stimulus. This may be illustrated by the following extract from my Laboratory Book descriptive of an experiment which a note added immediately after the observation characterizes as a very perfect case; there were absolutely no twitches to mar the firm tetanus of the ilio-coccygeals, and the lymph-hearts behaved exactly like ordinary striated muscle-nerve preparations.

Exp. IV. Frog decapitated. All nerves, except the tenth, divided. Abdominal viscera, etc., removed. Legs amputated. Back of 8th vertebral arch removed. Cord snipped across between 6th and 7th vertebræ. Non-polarizable electrodes placed in position as above described.

Time.	Distance between coils in cm.	Remarks.
h. m.		
3 7	30	No contractions whatever of any muscles.
	25	Contractions and twitches of ilio-coccygeal muscle of left side.
	22	Stronger contraction of ilio-coccygeal muscle: none of hearts.
	20	Still stronger contraction of ilio-coccygeal muscles of both sides, with no twitches whatever.
	18	Firm tetanus of ilio-coccygeal muscles, unmarred by any twitches whatever: no (?) movement of hearts.
	12	No movement of hearts; firm tetanus of ilio-coccygeals.
	10	Systole (tetanic) of hearts, just like that of neighbouring muscles.
	11	No contraction of hearts.
3 40		Repeated the above tetanic stimulation of hearts many times with exactly the same result, *i.e.* a firm tetanus of the hearts and surrounding muscles unmarred by any twitches whatever.

Such were the phenomena of hearts brought to complete standstill by separation from their spinal centres. The case of hearts still exhibiting movements after a similar separation* was substantially the same; viz. (1) a much greater minimal stimulus was required to affect them, than sufficed to affect the other nerve-supplied striated muscles; and (2) when that minimal stimulus had been reached, the stimulus caused the hearts, twitching vigorously before, to rush into systole, which gave place to vigorous twitchings again on discontinuing the stimulus.

But although the above experiment (IV.) may be regarded as a typical one when the irritability of the preparation and contact of the electrodes are absolutely perfect, yet I should say I have found considerable difficulty in securing such perfect conditions. Especially when working with non-polarizable electrodes applied to the nerves in the spinal canal, it is frequently the case that interrupted currents cause a brief systole of the lymph-hearts breaking at once into a series of movements which often curiously simulate beats. When using stimuli near the minimal strength for the lymph-cardiac nerves this is commonly the effect; and the firm tetanus of the surrounding muscles, to which the same strength of current is a most powerful stimulus, forms a very misleading contrast to the movements of the lymph-hearts. These movements are however never deliberate beats

* See the preceding paper, p. 6.

such as the ventricle of the blood-heart exhibits when stimulated by strong tetanizing currents; they are explosive in character even when full, and are most frequently confused or twitchy. Generally (but not always) it is possible by increasing the intensity of the current to drive the hearts into perfect systole, unless indeed their nerves are nearly exhausted; and it is always possible by such increase of stimulus to extend the duration of the tetanic systole invariably preceding the pulse-like movements. In short, the movements are not to be attributed to some peculiar organization of the lymph-cardiac muscles or nerves: they rather find their parallel in twitches such as the coccygeal muscles exhibited in Exp. IV., when the secondary coil stood at 25 cm.

I mention this source of fallacy because, though fully alive to its existence in the imperfect contact of electrodes or commencing exhaustion of the fibres stimulated, yet for some time I was under the impression that the lymph-hearts while connected with their spinal nerves could not be forced into tetanus except by exceedingly strong interrupted currents.

When experimenting on the direct stimulation of curarized lymph-hearts under the conditions described on page 21, there seemed to be reason for believing that the minimal stimulus of the curarized lymph-heart muscle was a slightly greater one than that of a curarized ordinary muscle. But I have not paid much attention to the point, and on reflection am not inclined to lay any stress on the observation; for the position of the lymph-hearts, surrounded by connective tissue and defended by muscular barriers presenting their fibres for the most part transversely to the electrodes, is quite enough to account for the slightly higher minimal stimulus they seem to require.

In the next place, the effect of the interrupted current on the acting spinal centre of the posterior lymph-hearts was observed. It is already known that there are inhibitory fibres in the spinal cord which, during life, constantly convey inhibitory stimuli from a centre in the encephalon, to the centre near the sixth vertebra. These fibres are to be found in the cord on the same side as the centre to which they are running: and they seem, like the inhibitory vagus fibres, to be, in the frog, easily exhausted*. Stimulation of the upper part of the cord after division of all spinal nerves except the tenth pair, can readily be shown to bring the lymph-hearts to rest in diastole, by merely placing a drop of strong salt-solution on the cord exposed, say, by decapitation. In a short time the hearts begin again to beat—at a time that is when the dorsal muscles supplied by spinal nerves as yet uncut are still in tetanic contraction.

* See the preceding paper, p. 12.

In exciting the active spinal lymph-cardiac centres the form of experiment was substantially that which has already been described. Instead of snipping the column across at the level of the seventh vertebra, windows were made into the spinal canal at the back of the fifth and eighth vertebræ, these relatively wide limits being taken to make quite sure that the centre was included between them*. The spinal column, resting on the abdominal viscera of the frog, was firmly pinned out to avoid curling backwards of the column in consequence of any escape of current to the dorsal muscles. The tips of non-polarizable electrodes, well softened with salt solution, were pushed in at windows; and the electrical arrangements were, as before, a Du Bois' induction apparatus with the secondary coil capable of being broken on the side of both electrodes, a plug-key in the course of the primary coil, and a single Grove's cell.

If ordinary platinum electrodes were to be used, the backs of the seventh, sixth, and fifth vertebræ were removed, and the cord was hooked upon the curved electrodes; or the electrodes were placed one on each side of the cord about the level of the sixth vertebra.

The beats of the hearts (usually of the one best to be seen) were counted, and checked by a watch whose face was kept in the same field of vision with the pulsating hearts.

Exp. V. Frog decapitated. All nerves divided except the tenth. Back of 5th and 8th vertebræ removed, non-polarizable electrodes well moistened with salt solution applied to cord.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
h. m. s.			
12 32		8—9	Normals just before applying electrodes.
		8	
		8	
12 35			Applied electrodes.
12 35 30		6—7	
		7	
		7	
12 38		6—7	
12 39	30	7	No contractions of muscles. Stimulated for 10 sec.
12 40	25	7—8	Ditto. Ditto.
12 41	22	7—8	Slight movement of coccygeal muscles. Ditto.
12 42 30	22	7	Ditto. Ditto.
12 43	20	7	Tetanus of coccygeal muscles. Ditto.

* The spinal centres of the posterior hearts possibly vary somewhat in position in the cord. See *An Account of the Anat. and Physiol. of Batrachian Lymph-Hearts* preceding this paper.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
12 44	13	4	Strong tetanus of coccygeal muscles. Ditto.
12 45		7—8	Normals.
12 45 20	17	4—5	Strong tetanus of coccygeal muscles. Ditto.
12 46	15	3	Ditto. Stimulated for 30 sec.
12 48	13		Muscles as before. Heart passed for several seconds and then gave a few rather rapid and hesitating beats.
12 49		7—8	Normals. Let rest for several minutes.
12 56		5—6	Normals.
		5—6	Normals.
12 57 30	10		Firm but not violent tetanus of ilio-coccygeals. Long diastole of hearts.
12 58 30	7		Muscles as before. Long diastole of hearts.
	0		Ditto. Ditto.
1 2	0		Muscles as before. Long diastole of more than 30 sec., then a series of hampered beats, slow and imperfect for the next minute (stimulus applied all the time), then stimulus discontinued; then quietness for 5-7 sec.; then beats quite normal in appearance.
1 5		4—5	Normals.
1 8		2·6	Normals.
	0		Strong tetanus of most of muscles of body. Current maintained for 3 min., during which time the hearts, now and then, tried to beat with full but hampered beats. On breaking stimulus the hearts continued to rest in diastole for 5 sec., and then beat
		0·5	quite normally 12—13 times in 20 sec. next succeeding.
1 20			Divided cord and spine in front of 8th vertebra. Applied electrodes, one to exposed end of cord, the other to the aperture in the 8th arch. Hearts quite still.
1 22 30	28		No muscular movements.
1 23	20		Ditto.
1 23 30	15		Ditto.
1 23 45	10		Twitches of ilio-coccygeal muscles and contraction of lymph-heart (the left was observed).
1 24	12		Systole of lymph-heart *without movements of any other muscle*. This is clearly due to the greater exhaustion of the ordinary muscles. This was repeated many times: the systole lasts 3—4 seconds, *i.e.* it is not a single beat, and gives place to perfect quiet.

Exp. VI. Frog decapitated. All nerves divided except the tenth. Back of 5th and 8th vertebral arches removed. Non-polarizable, well moistened, electrodes prepared.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
h. m. s.			
3 51 30		6—7	Normals.
		6	
		7	
		7	
3 56			Spine pinned out: electrodes applied.
		6·6	Normals.
3 58	18		Strong tetanus of ilio-coccygeals.
			Lymph-hearts pause for 10 sec. = 30 sec. of
		7·5	beat 15 in 20 sec. stimulation.
4 1	15		Lymph-hearts pause for 20 sec. = 30 sec. of
		7	beat 7 in 10 sec. stimulation.
4 3 30	13		Lymph-hearts pause for 20 sec. = 30 sec. of
		5	beat 5 in 10 sec. stimulation.
4 5	10		Lymph-hearts pause for 15 sec. = 30 sec. of
		5	beat 7-8 in 15 sec. stimulation.
4 10		5·6	Normals.
4 11	8		Strong tetanus of ilio-coccygeals and of whole of leg.
			Lymph-hearts pause for 20 sec. = 30 sec. of
		4 (?)	beat 4 (?) in 10 sec. stimulation.
4 13	8		Strong tetanus of ilio-coccygeals and of whole of leg.
			Lymph-hearts pause for 22 or 21 sec. = 30 sec. of
		5·8	beat 5 in 8 or 9 sec. stimulation.
4 15 30	8		Lymph-hearts pause for 15 sec. = 30 sec. of
		4	beat 6 in 15 sec. stimulation.
4 18	6		Strong tetanus of ilio-coccygeals and whole of leg.
			Lymph-hearts pause for 30 sec. = 30 sec. of stimulation.
4 20		3	Normals.
		3	Ditto.
		4	Ditto.
4 21	5		Strong tetanus of legs, etc., as above.
			Lymph-hearts pause for 2 min. (= whole time of stimulation) then give one full beat after stimulus had been broken; then hesitating beats at uncertain intervals.
4 25		2	Normals.
		3	
		2	
			Gave time for rest.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
4 32		1·6	Or 10 beats in the minute during which the hearts were counted.
4 35		1	Or 6—7 beats in the minute during which the hearts were counted.
4 36	5		Pause for 3 min. (= whole time of stimulation); then imperfect, hesitating beats for 1 min.; then occasional full beats with intervening flickers for some time.
4 50			1—2 beats a minute in the minutes during which the hearts were counted, and but few intermediate flickers.
4 54			Snipped spine across at level of 7th vertebra. Placed electrodes, one at exposed end of cord and the other at the aperture in the 8th arch. Hearts perfectly quiet.
4 55	18		No movements of muscles.
	17		Contraction of lymph-hearts, *but not of other nerve-supplied muscles.* (Due to exhaustion of the other muscles clearly.)
4 56 30	15		Distinct short tetanus of lymph-hearts, but not of any other muscles.
	10		Distinct tetanus of lymph-hearts, *together with contraction of other muscles.*

Exp. VII. Frog decapitated. All nerves divided except the tenth. Back of 5th and 8th vertebral arches removed. Non-polarizable, well moistened, electrodes prepared.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
h. m. s.			
1 24		7	Normals.
		8	Ditto.
		8	Ditto.
1 25 30			Electrodes applied: left heart stopped.
1 26 30			Left heart begins again.
		8	Normals.
		8	Ditto.
		8	Ditto.
1 28	12	5	Strong tetanus of ilio-coccygeals.

Time.	Distance between coils in cm.	Heart's rate in 10 sec.	Remarks.
1 29 30	10		Strong tetanus of ilio-coccygeals, and also of leg.
		0	Lymph-hearts beat 3 in 10 sec. } = 30 sec. of then pause for 20 sec. } stimulation.
1 31	10		Long diastole of heart: no doubt whatever about the diastolic nature of the pause.
	7		Long diastole.
	5		*Heart stopped in systole* for a few seconds and then flickers.
1 35			Noticed the hearts were not going.
1 39			On more careful inspection the hearts are found to be flickering occasionally.
1 40	4·5		Stimulated for 30 sec.; first came a systole; then flickers; then irregular spasmodic contractions; then the stimulus was shut off; after which the spasmodic contractions continue about 20 sec. longer than the stimulus; then the hearts became perfectly quiet. No twitches of neighbouring muscles.
1 42	4·5		Repeated exactly, with the same result except that the after-contractions only lasted 10 sec. No twitches of neighbouring muscles.
	3		Systole, followed by spasmodic irregular contractions as before.
1 48	0		Long systole of 12 to 15 sec.; then irregular, hampered, spasmodic contractions; and much better spasmodic contractions for a few seconds on discontinuing stimulation. Slight twitches of other muscles.
1 55			Divided cord and spine in front of 8th (across the 7th) vertebra. Placed electrodes, one against the cut end of the cord, the other at the aperture at the back of the 8th vertebral arch. No twitches of hearts or other muscles.
1 57	5		Contraction of ilio-coccygeals.
	3	}	? of hearts.
1 57 30	2	}	Long systole of hearts and neighbouring muscles: that of hearts giving way to flickers and irregular beat-like movements*.

* These are examples of the movements curiously resembling beats spoken of above when reviewing Exp. IV.

A review of the foregoing, and similar, experiments enables us to conclude:

That (1) the effect of interrupted currents on the lymph-cardiac spinal centres is an inhibition of the movements of the dependent hearts, and that the effect is more marked the stronger the currents.

That (2) the effect passes gradually from a slight slowing to a complete inhibition.

That (3) the inhibition by strong currents is sometimes perfect as long as stimulation lasts (as long as two or three minutes) (Exp. VI. $4^h\ 21^m$; $4^h\ 36^m$); but sometimes is marred by occasional beats which seem to be hampered or hesitating (Exp. V. $1^h\ 2^m$; $1^h\ 8^m$).

That (4) if the currents are made stronger a point may be reached at which the inhibitory effect is overborne, and the stimulus followed by contraction (Exp. VII. $1^h\ 31^m$, coil at 5 cm.). The strong currents necessary to cause prolonged inhibition, or to step beyond this and cause systole, speedily exhaust the spinal centres.

That (5) a stimulus strong enough to cause a slowing or diastolic pause of a lymph-heart whose spinal centre is intact, may be enough to cause tetanic systole when applied to the nerves of the same heart after the centre has been cut off (Exps. V., VI.) *.

That (6) the removal of the inhibitory stimulus sometimes but not invariably leads to a rebound of activity manifested in an acceleration of heart-rate (Exp. V. $1^h\ 8^m$).

The effect of the application of the pharmacopœal solution of sulphate of atropia both directly to the exposed cord, and indirectly by previous injection into the dorsal lymph-sac, was also tested. In neither way was any difference produced in the action of the interrupted current on the functioning lymph-cardiac spinal centre. At the same time it was observed that the application of saturated NaCl solution to the exposed upper end of the spinal cord of a frog poisoned by atropia in the dorsal lymph-sac, produced the usual inhibition of the lymph-hearts. Hence may be added to the results treated of in this section:

* It is true the electrodes in the latter case are closer together by about the depth of a vertebra than in the former, and hence the currents have less cord to traverse; but in both cases the electrode nearest the heart is in the same position.

That (7) the inhibitory powers of the lymph-cardiac inhibitory nerves are not abolished by atropia.

In addition to the above typical experiments many others were made with special reference to the passage from the inhibiting effect to the contracting or systolizing effect on increasing the strength of the currents. In these experiments, the details of which need not be given, the same doubt was encountered as in the experiments of stimulating the lymph-cardiac spinal nerves. There were, namely, two sets of results obtained, one set in which inhibition passed into perfect tetanus at once on increasing the current, and another set in which inhibition passed, not into tetanus, but into a series of twitchy or confused pulsations, which only culminated in a tetanus, if they did so at all, on still further increasing the currents. And the same question was here started, Are the confused twitches thus appearing as the firstfruits of the motor action of the currents, in reality due to the imperfect contact of non-polarizable electrodes and the commencing exhaustion of nerve-fibres? Are they, in fact, the analogues of the spasms which affect the ilio-coccygeals when their nerves are under minimal tetanizing stimuli applied to the spinal cord in the same way? My experiments lead me to believe that they are. They are never perfectly regular, deliberate beats; they are always heralded by a systole of several seconds duration—a systole the more prolonged the stronger the currents; they can generally be forced into unbroken tetanus by increasing the stimulus; and they are less frequent when the electrodes are platinum wires whose application admits of greater exactness, than can be obtained with the softened clay of non-polarizable electrodes.

No one will fail to be struck with the resemblance between the effects of the interrupted current on the inhibitory mechanism of the lymph- and blood-hearts. In both cases there are inhibitory fibres proceeding from an encephalic centre, and possessed of moderate powers of endurance*. In both cases stimulation of the region about the termination of the inhibitory fibres leads to enormously prolonged inhibition, which is occasionally marred by beats or series of beats†. And in both cases, by increasing the current, the inhibitory limit may be passed and effects produced dependent on the stimulation of quite

* I am speaking of the frog. A. B. Meyer (*Das Hemmungsnerven-system des Herzens;* also *Centralblatt*, 1869, No. 14, p. 216) has shewn that the dog's vagus is incapable of complete exhaustion.

† A. B. Meyer, *loc. cit.*

another order of mechanisms, namely the motor*. For the rest, both the peripheral end of the inhibitory apparatus, and the motor apparatus, would seem to be absolutely more robust in the blood-heart than in the lymph-heart†.

But a far more interesting comparison is that between the effects of interrupted induced currents on the lymph-heart centre and on the snail's ventricle. The snail's heart (*Helix*) is one of the pulsating structures whose nervous elements, if any exist, have as yet eluded the search of microscopists‡. Yet the application of induced interrupted currents to it has led to the observation of undoubted inhibitory effects§, which may be best recalled by means of the following summary by the observers: "The phenomena thus produced [*i.e.* that an interrupted current applied directly to the heart of the common snail removed from the body will cause diastole] are altogether similar to those seen when the vertebrate heart is inhibited by stimulation of the pneumogastric nerve."

"This inhibition by direct stimulation requires a current weaker than is sufficient to cause a tetanus of the heart. It may be witnessed on either auricle or ventricle, and is the more easily obtained the more quickly the heart is beating. It takes place whatever be the position of the electrodes; and we find that it is possible thus to inhibit not only the whole ventricle, but separate parts of a divided ventricle, provided these can be obtained, as they sometimes can, beating with a suffi-

* If the electrodes of the secondary coil be placed about the *sinus venosus* and the coils gradually approximated, the inhibitory effect of the current, most marked with a distance (say) of 10 cm. between the coils, suddenly changes into a motor effect, causing rapid contractions, when the distance between the coils is still further lessened.

† The different action of atropia remains however as a striking distinctive character.

‡ F. Darwin, *Journal of Anatomy and Physiology*, Vol. x. Part iii. p. 506, "On the structure of the Snail's Heart." Mr A. S. Lea, who at Dr Foster and Mr Dew-Smith's request, examined the snail's heart with a view to discover nerves if possible: referred to in a paper by Foster and Dew-Smith, "On the behaviour of the Hearts of Mollusks under the influence of electric currents." *Proceedings of the Royal Society*, No. 160, 1875; also in *Studies from the Physiological Laboratory in the University of Cambridge*, Part ii. p. 73. Considerable doubt must, however, be entertained as to the freedom of the snail's heart from nerve-structures, since the publication of Dogiel's paper entitled "Die Muskeln u. Nerven des Herzens bei einigen Mollusken," in the *Arch. für Mikr. Anat.* Vol. 14, Heft i. But see Foster and Dew-Smith's notice with the same title in the same publication (Vol. 14, Heft iii. p. 317); and another paper by Dogiel, called "Die Ganglien-zellen des Herzens bei verschiedenen Thieren und beim Menschen," also in the *Arch. für Mikr. Anat.* Vol. 14, Heft iv. p. 470.

§ Foster, *Pflüger's Archiv*, Vol. v. p. 191. Foster and Dew-Smith, *Proceedings of the Royal Society*, loc. cit. *Studies*, loc. cit.

ciently rapid rhythm." And again*, "Moreover this inhibitory effect [of rapidly repeated induction shocks], this prevention of the contraction or beat, increases with the strength of the current employed, up to a certain limit, and then the action of the stimulus is suddenly reversed and a contraction or beat is caused instead of prevented. . . . In our results we pass at once from the maximum of inhibition to contraction."

Thus we have the curious result that the same stimulus produces in each case similar effects when applied (1) to a pulsating muscle apparently destitute of nerves, (2) to a pulsating organ whose nerves and muscles are inseparably blended, and (3) to the remote nervous centre (or part of centre†) of a pulsating muscle which, when taken separate from its nerves, behaves like any other undoubtedly nerveless muscle.

The bearing of this comparison upon the question of muscular functions as illustrated by the hearts of Frogs and Snails, need not specially be enforced. It must indeed be confessed that analogy in physiological questions like the present, is not very fruitful of trustworthy inference, for we have only to look around us to find numerous examples of one tissue with many functions. But besides this, our knowledge is even yet far from being wide enough. Can the movements of the ureter be inhibited by weak interrupted currents, like those of the snail's ventricle? Both the ureter‡ and the snail's heart§ are said to exhibit a tetanus; but is it more difficult to be caused in them than in corresponding non-pulsating muscular tissues? Did we possess the answers to these questions, we might have greater assurance in drawing inferences. It will be well therefore to leave the matter for the present, calling attention to the undoubted fact, that the peculiar reaction of the lymph-cardiac apparatus to interrupted currents, is a property of its nervous elements, and not of its pulsating muscle.

ii. On the Action of Constant Currents.

It would, perhaps, be wise to call the following part of this paper a preliminary communication, since I have not as yet had time to work out carefully the points started. It shall, at least, be preliminary in

* *Studies*, p. 80.

† Of which the other part may be in the neighbourhood of the hearts themselves. See the preceding paper.

‡ Engelmann, *Pflüger's Archiv*, III. p. 247. (See *Centralblatt*, 1870, p. 471.)

§ Foster, *loc. cit.*

the sense of containing statements of facts, rather than offers of explanation.

In examining the action of the constant current on the lymph-cardiac mechanisms, the following procedure was adopted. The frog was prepared, as if for experiments with interrupted currents (p. 20), by decapitation, reflection of the skin over the back, removal of the abdominal walls and viscera, and amputation of the thighs. The frog was pinned down to a cork table, capable of being raised and depressed by a fine screw. The battery consisted of a number of small Daniell's cells or large Grove's cells; and the electrodes were non-polarizable and of the ordinary type. In the current was placed a commutator, and between the commutator and the battery, a cup of mercury to serve as a key.

Direct application to the beating Lymph-hearts.

The electrodes were applied at the ends of a line passing through the lymph-hearts, just where the stumps of the thighs joined the pelvis: or they were applied to the posterior surface of the pelvis, one near the lower or anal extremity of the lymph-heart, and the other near the upper extremity, or a little above the upper extremity, of the same heart. In the former plan, the currents passed (it is assumed) transversely across the hearts, one of which would be anodic, while the other would be kathodic. In the latter plan, the currents passed longitudinally up or down the hearts, while the subjacent ilio-coccygeus muscle with the dorsal and abdominal branches of the tenth spinal nerve, would be alternately anodic and kathodic, according as the current was running.

As far as my experiments have gone, in whichever way the current is flowing, and with a battery strength of from 6 to 12 or more small Daniell's, the beating of the lymph-hearts is hampered or inhibited. The rhythm of the beats in the former case is not altered, the depth or fulness only being modified.

Direct application to Lymph-hearts stopped by separation from their spinal centres.

Preparations were made as if for the above experiment on the beating hearts, but the spine was snipped across, between the 6th and 7th vertebræ; or the tenth, coccygeal nerve was divided as it emerged from its foramen in the coccyx. Or, the lymph-heart was carefully excised with the connective tissue usually surrounding it, and placed

upon one electrode and touched by the point of the other. All strengths of battery were used, from 1 or 2 small Daniell cells to 18 large Grove's. But the lymph-hearts could not be induced to pulsate, or in fact, do more than reply to the opening and closing shocks. The position of the electrodes, when applied to the hearts *in situ*, was varied in all directions on the posterior surface of the pelvis; but no attempt was made to pass the current from the abdominal to the dorsal side of the hearts, or in the reverse direction. Neither was any regard paid to the position of the axes of the heart, on account of its small size in English frogs, when that organ was excised and placed upon the electrodes. I have not yet tried the corresponding experiments on the lymph-hearts of the tortoise.

Application to the lymph-cardiac spinal centre.

Preparation was made as before, but the backs of the 5th and the 7th vertebræ were removed, and the tips, well softened, of the non-polarizable electrodes were inserted through the openings thus made.

To the centre acting normally. Either an exciting effect, or a hampering and inhibiting effect, is caused by a battery-current from 1 or more Grove's cells. Either effect may occur with anode above or with anode below, in different frogs. In one frog the anode at the upper window may stop the hearts, while in another the anode at the lower window has the same effect; or the effect may be quite indifferent to reversal of the electrodes. Sometimes with a certain strength of battery the anode at either window inhibits, while a diminution in the battery-power may transform one or other position of the anode into a favourable rather than an unfavourable sign. While I cannot of course speak positively, I have very little doubt that the known electrotonizing powers of the constant current, with the known shifting of the neutral line as the battery is strengthened, together with the assumption of a stimulating action of the current, *per se*, on the lymph-cardiac centre, will account for all the facts. For example, with the electrodes placed as above described opposite the 5th and 7th vertebræ, and with weak currents in which the neutral line is near the anode, it is conceivable how reversing the current should be unable materially to alter the favourable katelectrotonus surrounding the lymph-cardiac centre, the neutral line skipping from one pole to the other on reversal, over the head, so to speak, of the motor-centre. Hence we must simplify the conditions by placing one electrode in the aperture through the

7th vertebra, and the other at the anterior extremity of the cord, in order to make sure that the region of the lymph-heart centre is distinctly anodic or kathodic. By doing so, we can get indications that it is not merely by overshadowing the lymph-heart centre with kat-electrotonus that the constant current produces its exciting effects, but also by exerting a special stimulant power that may work in spite even of anelectrotonus.

To the centre at rest from exhaustion. If a preparation like that described in speaking of the action of the constant current on the acting centre be allowed to remain exposed, the rate of the lymphatic hearts quickly declines, and the hearts finally come to rest. But the lymph-cardiac centre and nerves are not necessarily dead; they may usually be wakened into rhythmical activity by the passage of the constant current up or down through the centres. The pulsations are, as a rule, regular, more regular in fact than those which follow the passage of the same current through acting centres; and their appearance or non-appearance seems capable of the same degree of explanation as in the case last discussed.

To the centre brought to rest by stimulating the upper end of the exposed cord with saturated Na Cl solution. When lymph-hearts are brought to rest by the application of saturated Na Cl solution to their inhibitory fibres, currents which readily set the same hearts beating after their spinal centres have become exhausted, utterly fail to move them. I am not certain that very stong currents (I used 5–6 Grove's cells) cannot do so; but in the case of such strong currents, the anode must be above the lymph-cardiac centre for obvious reasons. In this position the anodic region would intercept and dissipate the inhibitory stimuli proceeding from above, and such an effect would of itself lead to renewed pulsation of the hearts.

CONCERNING THE EFFECTS ON THE HEART OF ALTERNATE STIMULATION OF THE VAGI.

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(*From the Physiological Laboratory of Owens College.*)

INTRODUCTION.

IN the summer of 1875 M. de Tarchanoff explained to one of us in person the results of an interesting experiment, which was subsequently published in the *Archives de Physiologie* (Série II. Tome II. 1875) as a "Note sur l'effet de l'excitation alternative des deux pneumogastriques sur l'arrêt du cœur." Par Jean Tarchanoff et G. Puelma. In this Note the methods of experiment and the results are thus set forth:

"Nous mettions à nu les deux pneumogastriques, et nous prenions leurs bouts périphériques à l'aide de ligatures. Pour observer les battements du cœur, nous introduisions par un trou, fait entre la cinquième et la sixième côte, un doigt dans la cavité du thorax, de manière à sentir directement les mouvements du cœur.

"Cette méthode d'observation est préférable à celle faite avec un manomètre, puisque cette dernière est sujette à erreur à cause de la coagulation du sang dans les canules.

"Si l'on excite longtemps un des pneumogastriques du chien avec des courants forts jusqu'à épuiser complètement son action sur le cœur, ce qui se manifeste par le retour de ses battements, et si l'on passe immédiatement à l'excitation de l'autre on n'obtient plus d'arrêt du cœur, et même en n'observe aucune alteration de son activité: et pourtant le nerf excité en dernier lieu n'est alors, on le conçoit, nullement épuisé.

"Le fait inverse se produit si l'on excite ce dernier nerf pneumogastrique (non épuisé) une à deux minutes après la cessation de l'excitation du premier. On observe immédiatement l'arrêt du cœur.

"Cette expérience indique nettement que chacun des pneumogastriques met en jeu tout l'appareil modérateur situé dans les parois du cœur; et qu'une fois cet appareil épuisé par l'excitation d'un pneumogastrique, il ne peut être mis en activité par l'excitation de l'autre."

In October, 1876, one of us made an experiment on a rabbit to test the above-described result. The vagi were exposed and divided under chloroform. Their peripheral ends were seized with ligatures. Stimulation was effected by an interrupted induced current from a Du Bois-Reymond's induction coil, the primary coil having a bichromate battery of one cell in connection with it. In the secondary coil a commutator was interposed for the purpose of rapidly shunting the current from one vagus into the other. Means were taken to record the heart-beats and blood-pressure from the femoral artery. Under the conditions of this experiment results were obtained which seemed to compel an important limitation in the statement of Tarchanoff and Puelma's facts, and a total rejection of their mode of explanation. It was found that continued stimulation of one vagus never annulled, or even prejudiced, the inhibiting powers of the other, unless the inhibiting apparatus had been recently kept under stimulation for some time. We may at once say that numerous experiments made at a later date, on dogs and rabbits, fully established this result.

Circumstances prevented our following up the research at that time; but during the past year the wished-for opportunity occurred, and we began together to extend the experiments to frogs, as well as to rabbits and dogs. While doing so we received Marey's *Physiologie Expérimentale* (II Année, 1876), containing an account of experiments by M. de Tarchanoff, entitled "Innervation de l'appareil modérateur du cœur chez la Grenouille" (p. 289). In this paper, besides other experiments and conclusions which do not concern us now, de Tarchanoff states that the behaviour of the frog's heart to vagus-stimulation is quite different, in respect of the mutual influence of the two nerves, from the behaviour of the heart of dogs and rabbits: "J'ai vu alors que si l'on attend pour exciter le second pneumogastrique que le premier ait été épuisé par l'excitation, l'arrêt du cœur s'obtient de la façon la plus nette;" and he concludes: "Que chez les mammifères (dog, rabbits) les deux nerfs aboutissent à un appareil modérateur commun, tandis que, chez la grenouille (Rana esculenta) chaque nerf aboutit à un appareil indépendant."

We found that, in the frog (R. temporaria), just as in the mammal, stimulation of one vagus never annuls, or ever prejudices, the inhibiting powers of the other, unless the inhibiting apparatus have been recently kept under stimulaton for some time; but we by no means feel ourselves driven to the same conclusion as de Tarchanoff. We may, in brief, define our opposition to the latter as a limitation of

his facts as regards both mammals and batrachians, and a rejection of his theory of explanation.

With regard to the principal fact announced by de Tarchanoff, viz. that it is impossible to maintain continuous cardiac diastole in mammals by alternate excitation of the vagi, it had been clearly stated by A. B. Meyer in 1869, in the memoir to which we shall make more lengthened reference at a subsequent part of this paper.

We shall now proceed to state the results of our own experiments.

Notes of Experiments.

On Dogs.

I. Small Dog. Rendered insensible by morphia-injection and inhalation of chloroform. Both vagi exposed in the neck. Cannula in right femoral for kymographic tracing.

Part I.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
	14	160	Normals before dividing vagi.
	14—15	174	
			Interval of about 5 min., during which the vagi were divided with scissors.
	34	144	Normals several minutes after division of vagi.
0	33	144	Stimulated right vagus. Interrupted induced current. 1 Daniell. Secondary coil 2 c.m. from primary. Platinum electrodes under each vagus. Commutator in secondary circuit for passing rapidly from one vagus to the other.
5	0	46	
17	0	28	
25	7	80	
70	11	100	
76	11	106	Shunted current into left vagus.
85	4	60	
100	5	66	Ceased stimulating.
110	40	160	Pulse at once rose, as did also the blood-pressure; both were irregular.
230	26	148	Pulse and blood-pressure subsided into steady curves.
248	26	154	Stimulated left vagus. Electrical conditions as before.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
258	0	40	
290	5·5	70	
355	9	100	Shunted current into right vagus.
360	5	80	
380	5·5	70	
423	9	100	Shunted current into left vagus.
433	4	80	
445		82	Ceased stimulating.
460	16·5		
470		120	

A clot here formed in the cannula connected with the femoral artery, causing a delay of about 12 minutes. After removing the clot the experiment was continued.

Part II.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
	36	130	Normals after removal of clot.
	36	146	
		132	
0	36	136	Stimulated right vagus; electrical conditions as before.
10	0	34	
63	0	24	Heart remained stopped an abnormally long time; on gently squeezing the chest of the dog the heart recommenced.
73	9	94	
93	10	100	Shunted current into left vagus.
103	4	60	
133	5	66	Shunted current into right vagus; no change whatever followed.
143	5	66	Ceased stimulating.
150	30	140	
230	29	136	

An interval of 50 seconds elapsed; when the experiment was continued.

Part III.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
		140	
	30	134	Normals after 50 sec. interval.
	30	140	
0	30	140	Stimulated left vagus. Electrical conditions as before.
5	0	50	
15	1	34	
40	4·5	60	
200	8·5	84	
300		100	Shunted current into right vagus; a clot had been forming just before which obscured the heart-beats: a distinct fall of pressure followed the shunting of the current into the
307		84	right nerve, but the heart-beats could not be seen.
340			Ceased stimulating: clot formed.

An interval of 13 minutes elapsed, during which a clot was removed. The experiment then continued.

Part IV.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
	35	120	Normals after removal of clot.
0	36	120	Stimulated left vagus: electrical conditions as before.
4	0	46	
21	1	26	
110	6·5	64	
123	6·5	60	Shunted current into right vagus. No change whatever occurred.

The records of the first and second parts of the foregoing experiment are contained in the subjoined diagrams, Plate I. Figs. 1 and 2, which shew at a glance the extent and effects of the several vagus-stimulations. The abscissæ denote time in seconds. The ordinates denote variations in rate of pulse in 10 seconds. The brackets at the foot

denote the time during which each vagus was being stimulated: the letters (R. L.) indicating the right and left vagus respectively. Further explanation, if needed, must be sought in the notes of experiment just set forth.

Note. It will be observed that, in this experiment, we were satisfied with the same signs of exhausted inhibitory power as satisfied de Tarchanoff; that is to say, we stimulated one vagus "jusqu'à épuiser complètement son action sur le cœur, ce qui se manifeste par le retour de les battements" (*vide supra*). But, although this experiment may well serve to cast doubt upon de Tarchanoff's statement, we are quite prepared for the obvious criticism, that the intermediate apparatus was not completely exhausted; that, in short, had we waited for complete exhaustion before shunting into the second nerve, we might have witnessed a failure of the vagus to inhibit. In subsequent experiments we were careful to meet this objection by allowing the heart's rate to reach the normal before shunting the current, or, at least, to approach the normal more closely than in the experiment just concluded. In rabbits the return to the normal was speedily effected; in dogs too slowly ever to allow of our quite reaching it.

II. Small Dog. Rendered insensible by morphia-injection and ether-inhalation. Both vagi exposed in the neck. Cannula in left femoral for kymographic tracing.

Part I.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
	34	146	Normals.
0	35	152	Both nerves on electrodes ready for stimulating. Stimulated left vagus. Interrupted induced current from Du Bois's machine worked with 1 Daniell. Secondary coil 6 c. m. from primary. Commutator in secondary circuit for shunting current from one to the other vagus.
4	0	90	
7	6·6	70	
17	16	116	Ceased stimulating. Blood-pressure rose to great height and heart rapidly became normal.
20	28	128	

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
27	30	178	Shunted current into right vagus.
40	0	20	
70	0	10	Heart began again to beat.
75	9	92	
95	13	128	
98	13	130	Shunted current into left vagus.
110	0	30	
120	2	12	
130	16	128	
150	17	148	Ceased stimulating, as a clot was forming in the arterial cannula.

An interval of 10 (?) minutes elapsed, during which the clot was removed.

Part II.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m. m. Hg.	Remarks.
			Electrical conditions as before: more ether administered.
0	36	158	Stimulated right vagus.
7	0	28	
20	8	94	Pulse remarkably large.
55	15	134	Pulse becoming smaller.
66	16	136	Shunted current into left vagus.
69	0	52	Heart began again.
79	10	80	
85	13	112	
120	17	142	
180	19	150	Shunted into right vagus.
185	0	46	
202	0	20	
205	12 (*i. e.* 3 beats since last observation)	86	Shunted into left vagus. (No inhibition followed.)
212	14	158	
220	24	146	Ceased stimulating.
250	22	148	

An interval of about 10 minutes occurred, during which a clot formed and was removed.

Part III.

Time in seconds.	Pulse in 10 sec.	Blood pressure in m. m. Hg.	Remarks.
		144	
	32	156	Normals after removing clot. Electrical conditions as before.
0	32	142	Stimulated left vagus.
4	0	40	
8	10 (*i.e.* 4 beats since last observation)	106	Shunted current into right vagus.
12	0	34	Heart began to beat again.
18	5 (*i.e.* 3 beats since last observation)		
28	6·5	80	Shunted current into left vagus.
31	0	44	
38	8 (*i.e.* 5·5 beats since last observation)		
72	10	100	Shunted current into right vagus.
80	0	18	
90	0	12	
96	5	74	Shunted current into left vagus. (No inhibition followed.)
122	10	126	Shunted current into right vagus.
130	7	80	Pulse large.
161	19	154	Pulse smaller. Shunted current into left vagus.
164	0	60	
171	8.5 (*i.e.* 6 beats since last observation)		
190	17	160	Shunted current into right vagus.
196	0	34	
216	0	12	Heart began again.
223	7	100	Shunted current into left vagus. (No inhibition followed.)
241	17	152	Ceased stimulating.
250	20	170	
300	21	166	

The records of this experiment are tabulated, Plate I. Figs. 3, 4 and 5, in the manner of the last diagram. In addition, however, we subjoin an actual kymographic tracing (woodcut, Fig. 1), taken at a peculiarly illustrative stage of the experiment; it corresponds in point of time to Fig. 3, Exp. II. pt. i.; in the latter, however, the effect of vagus-stimulation on the heart-beats and not on the blood-pressure being tabulated.

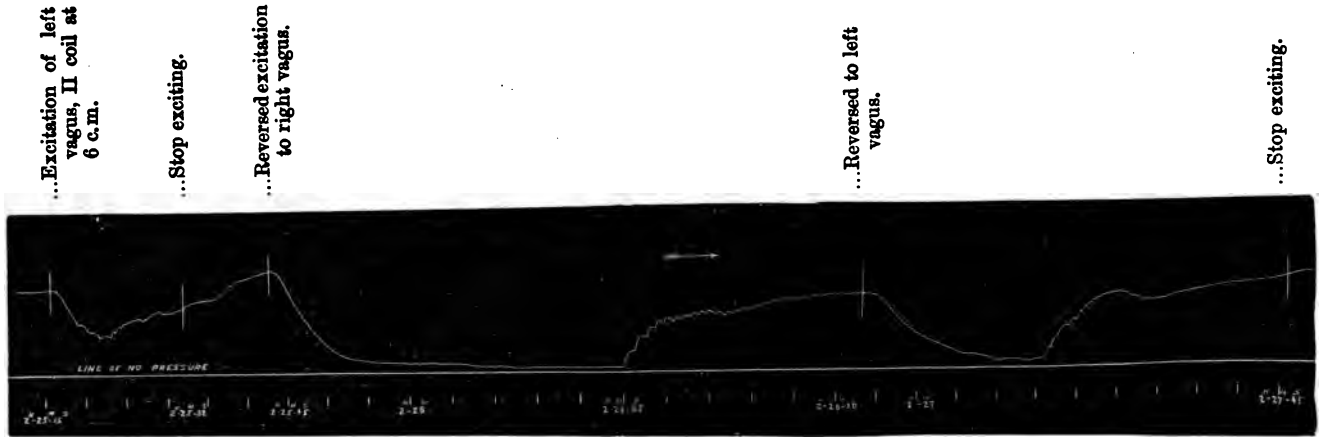
On Rabbits.

III. Rabbit. Both vagi exposed in neck under chloroform. Kymograph at femoral artery.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in m.m. Hg.	Remarks.
	34	134	Normals.
0			Stimulated right vagus with interrupted induced current. Distance between coils not noticed: bichromate battery.
5	8	70	
20	5	76	
40	11	120	
50	44	160	
70	43	154	
82	44	164	Shunted current into left vagus.
87	0	66	
90	2	42	
105	10	90	
120	20	130	Pulse made up of alternate long and short beats.
130	47	154	Pulse suddenly became normal, *i.e.* the alternate long beats disappeared and gave place to quite regular beats.
185	48	170	
195	54	162	Shunted current into right vagus. (No inhibition followed.)
200	48		
215	46	170	Ceased stimulating.
250	44	168	

A four-minutes interval occurred here, during which the heart spontaneously became irregular in its beating. (Was this due to some unseen stimulation of vagus trunks?) The subsequent record is therefore set aside as untrustworthy. A diagram of these results is shewn in Pl. I. Fig. 6.

Fig. 1 (Exp. II. pt. I.).


...Excitation of left vagus, II coil at 6 c.m.
...Stop exciting.
...Reversed excitation to right vagus.
...Reversed to left vagus.
...Stop exciting.
LINE OF NO PRESSURE

(Tracing reduced by photography to about $\frac{1}{3}$.)

The upper line is the tracing of the kymograph, the middle line is the line of no pressure, and the lower line is divided into intervals of five seconds. The tracing reads from left to right. Quite at the left of the figure a small portion of the normal tracing is represented. At 2h. 25m. 15s., a stimulus was thrown into the left vagus, the secondary coil being 6 c.m. from the primary. At once the heart stopped and the blood-pressure fell. The heart recommenced, and at 2h. 25m. 32s. the current was shut off from the nerve. It remained off about 10 seconds, and at the expiration of that interval the current was thrown into the right vagus. Again the heart stopped, and remained motionless until 2h. 26m. 25s., a period of 43 seconds, the current, of course, passing the whole of the time. The heart then began to beat, and the blood-pressure rose towards the normal rapidly. At 2h. 26m. 53s. the current was shunted out of the right vagus into the left, the nerve first stimulated, and once more the pulse ceased and the pressure fell. At 2h. 27m. 15s. the pressure quickly rose, notwithstanding the continued stimulation; until at 2h. 27m. 45s. the current was broken and the experiment brought to a close.

IV. Large Rabbit. Both vagi exposed in neck under ether. Kymograph attached to right carotid artery.

Part I.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in mm. Hg.	Remarks.
	47	106	Normals.
	49	104	Inhibitory powers of both nerves tested.
0	44	102	Stimulated left vagus. Interrupted induced current from Du Bois' machine. 1 Daniell cell. Commutator in secondary circuit to shunt from right to left vagus. Secondary coil 5 cm. from primary.
5	4		
14	0	30	Rabbit began to struggle.
29	8·6	140	
52	35	110	Shunted current into right vagus.
57	0	46	
62	(normal for a few beats)	140	No struggle occurred *.
80	0	32	Struggling begins.
105	7	80	
119	18	148	No struggling.
135	39	128	Shunted current into left vagus.
140	4	60	
170	15	100	
218	19	106	Shunted into right vagus.
221	36	120	
229	34	112	Shunted into left vagus.
231	14	88	
240	14		
243	16	100	Shunted into right vagus.
247	30	110	
250	32	100	Ceased stimulating.
300	37	130	

Interval of four minutes elapsed, during which a clot formed in the arterial cannula and was removed.

* Was this sudden return to the normal due to temporary want of contact of electrodes?

Part II.

Time in seconds.	Pulse in 10 sec.	Blood-pressure in mm. Hg.	Remarks.
0	45	96	Stimulated left vagus. Secondary coil 4 cm. from primary.
5	4	60	
40	12·5	80	
77	18	90	
97	*(18)	92	Shunted into right vagus.
118	0	30	Struggles, during which the nerves slipped off the electrodes. The pulse and blood-pressure at once rose to a great height.

For diagram of Pt. I. of this experiment, see Pl. I. Fig. 7.

On Frogs (Rana temporaria).

(*We select this experiment from the Laboratory Note-Book as a type.*)

V. Destroyed brain in front of atlanto-occipital articulation; thrust stout glass rod down gullet; exposed both vagi, and placed each on a pair of platinum electrodes; prepared to stimulate them alternately with interrupted induced current from a Du Bois' machine, worked with 1 Daniell's cell, the current-equalizer not being used. Heart-beats counted by means of a watch.

N.B. The frog's muscles, cord and nerves were very irritable, slight accidental stimuli producing marked reflex muscular contractions.

Time.	Pulse in 30 sec.	Remarks.
m. s.		
	21	Normals 3 min. before beginning the experiment.
	22	
0 0	22	Stimulated right vagus. Secondary coil 6·5 cm. from primary.

* The pulse was obscured at this point, probably by an incipient clot: there is no doubt however as to the rate since the blood-pressure showed no fluctuation, and the incipient clot, if any were there, did not plug the cannula perfectly, as the subsequent fall of pressure testifies.

Time.	Pulse in 30 sec.	Remarks.
m. s.		
0 30	2	
1 30	6	
		Shifted secondary coil to 5·5 cm.
2 30	14—15	
3 0	18	Shunted current into left vagus.
3 15	0	
3 30	10	Very powerful beats.
		Stopped stimulating.
5 0	19	
14 0	16	
14 30		Stimulated left vagus.
14 55		Auricles twitched.
15 0	1	
16 0	5·5	A series of 11 beats occurred: after which the heart again stopped.
17 0	0	
18 0	0	
19 0	0	
20 0	0	Touched the heart 3 or 4 times with point of lead-pencil: each touch led to a weak contraction of whole heart.
20 45	2	Feeble beats.
22	4	
25	5	
25 45	5	Shifted coil to 2 (or 3) cm.: no change observed in rate of beats. Returned coil to 5·5 cm.
27 0	0	Heart beat 5 times very quickly and then spontaneously stopped.
28 0	0	Heart gave one feeble beat.
29 0	4—5	
30 30		Shifted coil to 3 cm.
31 30	5	No change of heart-rhythm.
41 30	9	
42 0	0	Shifted coil to 0 cm.
43 0	0	Heart stopped.
43 15	0	First returning beat.
44 0	7	
45 0	8—9	
46 0	10	
46 30	12	
47 0		Shunted current into right vagus. Heart stopped.
48 0	0	
48 30	0	First returning beat.
49 15	4—5	Rhythm irregular.
50 30	4—5	
51 0	10—11	
51 30		Shunted current into left vagus.
52 30	0	

Time.	Pulse in 30 sec.	Remarks.
m. s.		
52 40	0	First returning beat.
53 30	3—4	
54 0		Shunted current into right vagus. No inhibition occurred.
54 30	10	
57 0	12	
57 30		Shunted current into left vagus.
60 20	0	First returning beat.
61 0	9	
61 30		Shunted current into right vagus.
61 45	0	
61 55	0	First returning beat.
63 30	15	
64 0		Shunted current into left vagus. Two beats followed: then heart stopped.
65 0	0	
66 0	0	
66 30	0	First returning beat.
68 30	13—14	
69 30		Shunted current into right vagus.
70 0	0	First returning beat.
71 0	10	
71 45	10	
72 0		Shunted current into left vagus.
73 0	0	
74 15	0	First returning beat.
76 0	14—15	
76 15		Shunted current into right vagus.
77 15	0	
77 40	0	First returning beat.
79 0		Heart did not go on beating. Ceased stimulating. Heart did not at once go on.
80 0		Began to beat—sluggishly. Continues beating, but sluggishly.

To emphasize the identity of effect in the frog and in the mammal we have constructed a Diagram, Plate I. Fig. 8, of the above experiment, made on the principles of the previous Tables.

The abscissæ here denote time in minutes; and the ordinates, the rate of pulse in 30 seconds.

Besides working in the direct, simple, method of the last experiment, we made many other experiments on Frogs, in which we registered with accuracy the heart's rate, the lapse of time and the moments of stimulation and shunting. The heart's rate was indicated by means

of Marey's very handy *myographe du cœur**, the time by an electro-magnet and Ludwig's *Unterbrechungsuhr*, and the moments of stimulation by a marking key, each holding a pointed lever against a smoked revolving cylinder.

As the gain in rapidity of working led to slight, but suggestive, differences in the experimental results, it will be useful to give here a type of this series of experiments.

VI. Frog (*Rana temporaria*). Brain destroyed in front of atlanto-occipital articulation; vagi exposed and slipped over platinum electrodes; heart exposed and placed between the pans of the *myographe du cœur*. Arrangements made to stimulate the nerves, by means of Du Bois' induction machine, with an interrupted current: a battery of 1 Daniell's cell used.

Time in seconds.	Pulse in 5 sec.	Remarks.
	3	Normals.
0	3	Stimulated right vagus. Secondary coil 10 cm. from primary. Heart stopped after giving three slight beats.
30		Beats reappear, but are very slight, and about 3 in 5 seconds.
45		Beats again disappear.
95	2	Beats reappear, but are very slight.
140	2·5	Beats of full vigour. Shunted current into left vagus; heart stopped.
225		Slight beat noticed.
235	2	Beats rapidly becoming stronger.
250	2·25	Beats of normal vigour.
260	2·5	Shunted current into right vagus.
270	2·5	Beats weaker than before.
295	2·5	Beats very slight.
360	2·5	Beats very slight.
375	2·5	Beats stronger, but not so strong as normal. Shunted current into left vagus.
		Heart stopped.
410		Heart begins to beat very faintly.
415	2·5	Beats very faint.
455	2·5	Beats of normal vigour. Shunted current into right vagus.
		No stoppage: heart beats become slight.
470	2·5	Beats very slight.
495	2·5	Vigour of beats almost normal.
		Ceased stimulating.

* See Marey's *Physiologie Expérimentale*: II. Année 1876, p. 70.

The important portions of the record are shewn in Fig. 2 on the opposite page. The experiment reads from right to left, and from above downwards. Portions of the tracing have been omitted to save space. Thus between (I) and (II) 45 seconds of tracing are wanting; between (II) and (III) 70 seconds of tracing; and between (III) and (IV) 85 seconds of tracing. But in all cases the nature of the omitted part may be learnt by studying the neighbouring portions that are retained.

On comparing this experiment with the previous experiment on a frog, we may observe that while in the latter there was only one case of failure to inhibit in the part of a vagus in the course of a very long experiment, there are here two well-marked instances, viz. at the 260th sec. and at the 455th sec. This fact no doubt has reference to the longer time allotted to each stimulation (and, in consequence, to recovery of the resting nerve) in the former experiment than in the present.

CONCLUSION.

A review of the preceding figures and diagrams will at once justify our formulation of the results of our experiments. In all the animals hitherto examined (viz. dogs, rabbits and frogs) stimulation of the vagus never annuls, or even prejudices, the inhibitory powers of the other vagus unless when the inhibiting apparatus has been recently under stimulation for some time. It would therefore seem that de Tarchanoff, in asserting the mutual prejudicial action of vagus-stimulations in mammals and denying it in frogs, has missed one half of the truth in the case of the former, and the other half in the case of the latter.

The instances calling for the reservation made in our general statement will be discussed after we have offered our explanation of the phenomena. It will be enough now to point out where they occur in the tabulated experiments. They are to be found in: Exp. I. pt. ii. 133rd sec.; Exp. II. pt. ii. 205th sec.; Exp. II. pt. iii. 96th sec.; ibidem, 223rd sec.; Exp. III. 195th sec.; Exp. IV. pt. i. 218th sec.; ibidem, 243rd sec.; Exp. V. 54th sec.; Exp. VI. 260th sec.; ibidem, 455th sec.

It seems to us that the generally accepted theory of the connection of the vagus nerves with a common intermediate apparatus is fully competent to cover the facts established by de Tarchanoff and ourselves. Each vagus abuts against a common nervous apparatus, through which every inhibitory stimulus must pass to reach the cardiac muscle.

Fig. 2 (Exp. VI).

Momentary escape of heart from vagus-control.

Stimulated right vagus: coil at 10 cm.

Shunted into left vagus.

Shunted into right vagus.

Shunted into left vagus.

Ceased stimulating.

Shunted into right vagus.

We have merely to suppose—and the supposition we shall presently see is not gratuitous—that the exhaustibility of the vagi is far greater than that of the common mechanism to which they lead in order to gain a consistent view of the facts. When one vagus is stimulated with a strong current the heart, after a longer or shorter period of diastolic rest, gradually escapes from the inhibitory influence of the stimulus. This escape must not be supposed to be due to the gradual exhaustion of the whole inhibiting apparatus, but merely to that of the vagus which is being stimulated. The heart escapes, not because its guard is enfeebled, but because the warrant for detention miscarries. On shunting the current into the other vagus the intermediate apparatus is at once roused and the heart stopped. So much greater is the "staying power," so to speak, of the intermediate apparatus, that, even in the mammal, where we may fairly assume it to be more readily exhausted than in the frog, the intermediate apparatus seems capable of tiring out relay after relay of reinvigorated vagi. Nay, we may at once state our belief that it is next to impossible, by the most careful and judicious alternate stimulation of the vagi, to cause exhaustion of the intermediate apparatus; for, after stimulating the vagi alternately a few times, the interval during which each vagus can hold the heart in check becomes too brief for the recovery of the resting vagus. This we have repeatedly demonstrated on the frog; we have checked the heart through one vagus, and on the first sign of exhaustion in the shape of a beat, we have shunted the current into the other vagus; again, when the latter had become exhausted we have shunted back into the first vagus. In the early parts of the experiment the intervals during which the second vagus held the heart in check was long enough for the first vagus to recover its controlling power; but after a few trials the intervals became shorter and shorter until the experiment was reduced to a series of rapid shuntings from one vagus to the other. Then the heart bade defiance entirely to the current, and beat normally. And we have thereupon shown that this normal beating was not due to exhaustion of the intermediate apparatus, by applying a current to the *sinus venosus*, when the heart invariably stopped dead, even if the current so applied were slighter than that passing through the vagus nerves. But, although we believe that the intermediate apparatus can, in health, easily wear out the organized attacks of the vagi, particularly in the case of frogs; yet we think it not improbable that, in conditions unfavourable to the restorative processes, the intermediate apparatus may occasionally succumb to successive vagus-stimulations, especially

in the case of mammals. This, however, we are convinced, very rarely occurs; and we believe that the majority of the cases for which the reservation in our general statement was framed, are due to exhaustion, not of the intermediate, common, apparatus, but of the particular vagus nerve which fails to check the heart. Let us examine the special cases which appear in the diagrams. It is clear that failure to check the heart might be due either (1) to complete exhaustion of the vagus nerve stimulated, or (2) to complete exhaustion of the intermediate mechanism. If it were due to exhaustion of the intermediate mechanism, the current, when applied immediately afterwards to the opposite vagus, should be equally ineffectual to stop the heart. If it were due to exhaustion of the vagus nerve, the shunting of the current from the active nerve into the exhausted nerve should have exactly the same effect on the heart's rate as shutting off the current altogether; thus, for example, the emancipation of the heart from vagus control, if not complete before, should at once become complete on turning the stimulus from the vigorous into the exhausted nerve.

Turning now to the first case of failure to stop the heart on shunting the current into a vagus which had shortly before been under stimulation (Exp. I. pt. ii. 133rd sec.), we find that the effect of the shunting was not to stop or slow the heart, but merely to arrest the gradual escape of the heart from vagus control. Here clearly both nerve and intermediate apparatus were active; but since the nerve was certainly not in full vigour, having only 40 seconds before been severely tried, we probably shall not err in assigning to the exhausted nerve the responsibility of the failure; at least we cannot say it was due to exhaustion of the intermediate apparatus alone.

In the second case (Exp. II. pt. ii. 205th sec.) shunting into the left vagus was at once followed, not by stoppage or slowing of the heart, but by complete emancipation from vagus control, and a rise to what, at this stage of the experiment, had become the normal pulse-rate. It is, therefore, clear that the vagus nerve was entirely to blame.

Again in Exp. II. pt. iii. at the 96th sec., and at the 223rd sec., shunting into the left vagus—it is the same vagus in both cases—resembled exactly the cessation of stimulation.

In Exp. III. 195th sec., shunting into the right vagus, which had readily checked the heart not long before, failed to produce any effect whatever*. Here the heart, during the prolonged stimulation of the

* It is quite true that a sudden slight fall of pulse-rate, such as occurred at the 156th second, chanced to coincide with the act of shunting, but the acts are evidently in no way connected.

left vagus, had completely escaped the inhibiting influence of the stimulus; we have therefore no reason to suppose that the failure was due to anything but exhaustion of the intermediate apparatus, especially when, later on, it was shewn* that the heart after a short season of complete rest, could be readily inhibited through the right vagus.

In Exp. IV. pt. i. 218th sec., and 242nd sec., in both which cases shunting into the right vagus at once let the heart slip from vagus control, the fault was without a doubt in the nerve.

In Exp. V. 54th sec. shunting into the right vagus did not slow or stop the heart, but rather let the heart go more quickly. This is somewhat inexplicable, since the right vagus never failed again in the course of the very long experiment. But, whatever the cause may have been, it certainly was not complete exhaustion of the intermediate apparatus; for the latter had been active just a second before, and stimulation of the other nerve (the left) $3\frac{1}{2}$ minutes after caused not merely stoppage, but a very prolonged stoppage, of the heart.

In Exp. VI. 260th sec. shunting into the right vagus did not stop, but merely enfeebled, the heart. This must have been due to failure of the nerve, and not to exhaustion of the intermediate apparatus; for, on shunting the current into the left nerve at the 375th sec., the heart was at once checked. About the failure at the 455th sec. we cannot speak so positively; but it is most probable the cause was again the exhausted state of the nerve.

In only one case, therefore, out of the above examples (which were taken without reference to this particular point), would it appear that the intermediate apparatus had been exhausted by successive alternate stimulations of the vagi. In every other case the enduring powers of the intermediate apparatus shewed themselves to be incomparably higher than those of the vagi.

The assumption of such enormous powers of endurance for the intermediate mechanism is not gratuitous. As long ago as 1869 A. B. Meyer† pointed out that the heart of the frog could be inhibited for hours by carefully applying interrupted currents to the *sinus venosus;*

* In a part of the experiment not published, for reasons already given: see Exp. III.

† A. B. Meyer, *Das Hemmungsnervensystem des Herzens* (Abstract by Schiffer, *Centralblatt*, 1869, No. 14, p. 216). It is interesting to notice that in the serpent (*Tropidonotus natrix*), Meyer succeeded in maintaining an almost unbroken stoppage for hours by continued stimulation of one vagus only; and by alternate stimulation of the right and left vagus a stoppage which lasted until the death of the animal.

and, although we have sometimes failed to inhibit indefinitely—as did also Meyer—we have always found it possible to stop the heart for very long intervals by stimulating the *sinus venosus* even with weaker currents than had just before sufficed to exhaust simultaneously the inhibiting powers of both vagi.

In conclusion, we may point out how an important fact by which de Tarchanoff seeks to uphold his theory of a twofold intermediate mechanism in the frog's heart is equally consistent with our theory. If one vagus is stimulated so as to check the heart; and if, just before that vagus becomes exhausted, the current is shunted into the opposite vagus; the whole time during which the heart is checked will be found to equal the sum of the times during which each nerve can stop the heart with a full interval for rest. This clearly agrees with the view of two perfectly distinct, right and left, inhibiting mechanisms. But it equally well agrees with the accepted view of a common intermediate apparatus of much greater enduring powers than the nerves connected with it. For, as the strength of a chain is determined by the weakest link, so the more readily exhausted vagus determines the length of time during which the heart may be checked by exciting through it the common inhibitory centre.

EXPLANATION OF PLATE I. Figs. 1 to 8.

In figs. 1 to 7, the abscissæ indicate time in seconds, and the coordinates the number of heart-beats in 10 seconds. In fig. 8 the abscissæ indicate minutes, and the coordinates the number of heart-beats in 30 seconds.

In all the figures, *R* signifies stimulation of the right, and *L* of the left, vagus.

In fig. 7, the sudden rise of pulse-rate to the normal about the 60th sec. was probably due to a momentary want of contact between the electrodes and the nerve, such as might have occurred from a slight movement on the part of the animal.

FIG. 6. (Exp. III.)

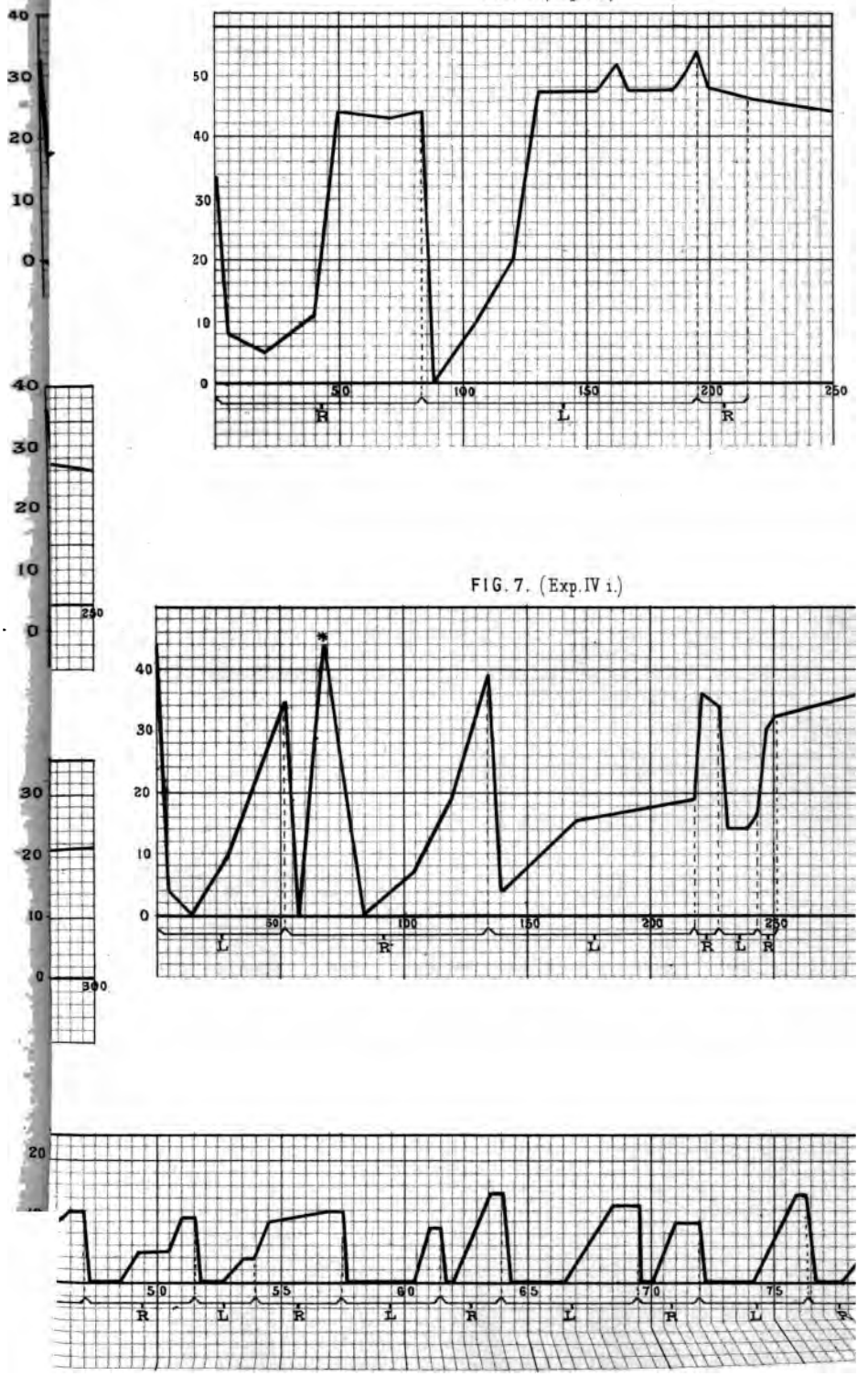
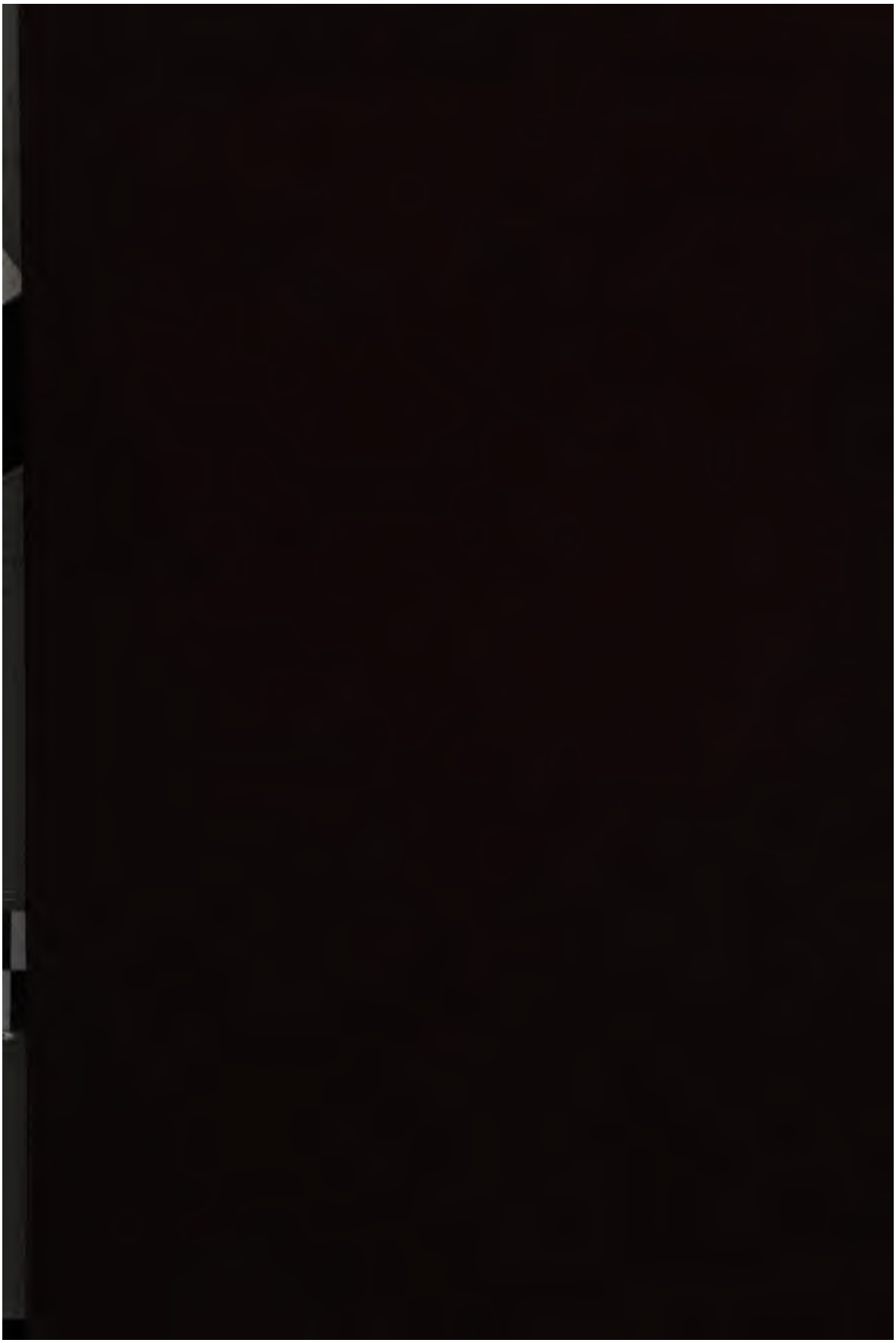



FIG. 7. (Exp. IV i.)